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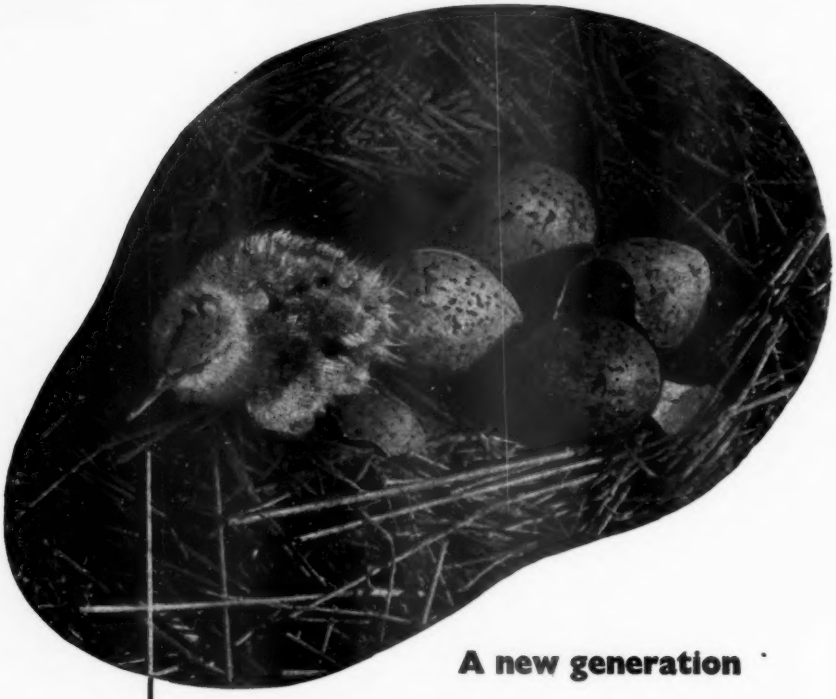

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# Section of Otology

President—Air Vice-Marshal E. D. D. DICKSON, C.B., C.B.E., M.D., F.R.C.S.Ed., D.L.O., Q.H.S.

[*November* 7, 1952]

## Some Effects of Intense Sound and Ultrasound on the Ear

### PRESIDENT'S ADDRESS

By Air Vice-Marshal E. D. D. DICKSON, C.B., C.B.E., M.D., F.R.C.S.Ed., D.L.O., Q.H.S.

*Senior Consultant and Consultant in Otorhinolaryngology, R.A.F.*

#### INTRODUCTION

THE trend of progress in this mechanical age is for greater speeds and power. We must therefore expect higher intensities of sound and a wider range of frequencies both airborne and structure-borne. Noise levels thus have increased both in our everyday existence and in some occupations to such an extent that resultant effects should be regarded as an occupational hazard.

#### DEFINITIONS

Noise may be defined as unwanted sound or, as the old gentleman said, "It is anything I don't want to hear". More precisely, audible airborne vibrations which produce a subjective impression of unpleasantness and discomfort to the listener constitute noise. The degree of annoyance depends on the sound-pressure level, the frequency distribution of the complex sound field, the duration of the sound and the susceptibility of the listener.

It would be helpful to define certain terms loosely applied to sound which are in current use, viz. Sonic, ultrasonic and supersonic. Sonic frequencies are those which are appreciated as sound by the human ear. They lie between 20 and 20,000 c.p.s. Frequencies about 20,000 c.p.s. are known as ultrasonic for they do not act upon the ear in such a way as to produce the sensation of sound. The term supersonic is used in reference to speeds greater than that of sound. In the problem of sound measurement there is a great deal of confusion caused by lack of agreement on basic terminology, reference levels and methods of measurement.

Physical sound is produced by an alteration in pressure, or displacement or velocity of particles in an elastic medium such as air. Sound waves in air under standard atmospheric conditions and at 68° F. travel at 1,125 feet per second or about 760 m.p.h.

When we make acoustical measurements of sound we usually measure its pressure rather than its amplitude of vibration. Intensity is a measure of the energy which is associated with sound and it depends on the amplitude or pressure.

Energy which is associated with the motion of air particles is proportional to the square of the amplitude of their movement (at a particular frequency or at any frequency) and to the square of the pressure or of the particle velocity in the displaced air mass or sound wave. Sound intensity may be defined as the rate of flow of sound energy through unit of area and is measured in watts per square centimetre. The reference level adopted as the standard for all acoustical measurements is the minimum audible intensity at 1,000 c.p.s., i.e. approximately an intensity of $1 \times 10^{-16}$ watts per sq. cm. This corresponds to a sound pressure of 0·0002 dyne per sq. cm.

The unit for comparing intensities is a "decibel" and is a ratio of power rather than an actual physical quantity. It expresses how much greater one sound intensity is than another. On this scale 10 decibels is a change of 10 times in intensity; 20 decibels a change of 100 times, 30 decibels a change of 1,000 times and so on. When a sound is halved in intensity the decrease is 3 decibels, i.e. 3 decibels is equivalent to the half-intensity unit.

By intense sound I mean sound that is strong enough to be perceived by some sense other than hearing. For example nasal cavities, sinuses, the opened mouth, may resonate strongly in an intense sound field. At 120 decibels all airborne sound stimulates significantly the sense of touch especially if it is assisted by resonance of some particular structure. It is at 120 decibels then that we begin to feel sound and the ear experiences discomfort.

#### METHODS AND MEANS OF MEASURING SOUND AND ULTRASOUND

To ascertain the component vibration or frequencies in a complex sound wave we use wave analysers by which an analysis may be made (in as much detail as desired). It is possible to use a narrow band filter of say 5 cycles per second by which the frequency range is covered in 5-cycle intervals. It is quicker and more practical, however, to use filters of wider band width for which

we employ Octavo Band Analysers. These cover the frequency range 40–10,000 c.p.s. in octave intervals. Fig. 1 illustrates a spectrum analysis of an aircraft engine.

To measure the overall sound pressure level a Sound Level Meter is used. A Sound Level Meter to simulate the response of the human ear over the entire frequency and intensity range would have

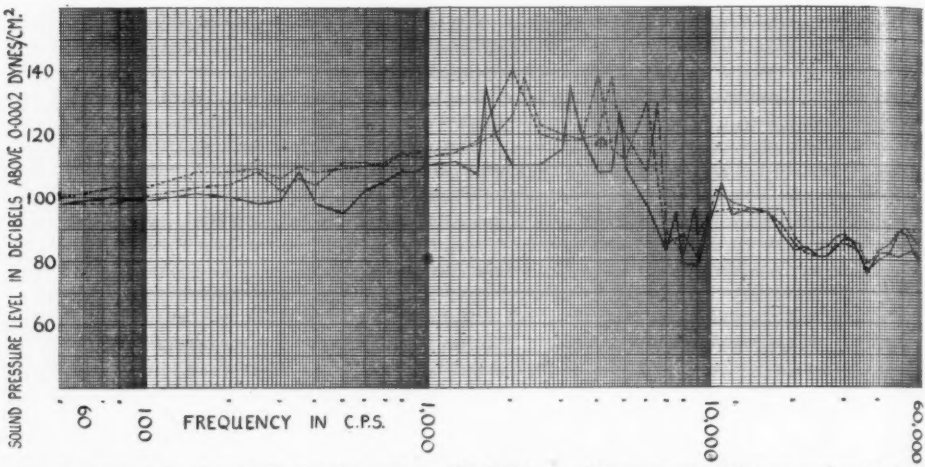



FIG. 1.—Narrow band analysis of noise spectrum (60–60,000 c.p.s.) from ghost turbine on engine test bed. Microphone on axis of engine and six feet in front of air intake.
———— 5,000 r.p.m. – – – – – 6,000 r.p.m. —·—·—·— 7,000 r.p.m.

to be a complex and bulky piece of equipment. To overcome this difficulty they are constructed with three response *versus* frequency characteristics:

(*a*) Flat network or one which simulates the ear's response to high level sounds.
(*b*) 70 decibel network or one which simulates the ear's loudness response curve to a stimulus of 70 decibels.
(*c*) 40 decibel network or one which simulates the ear's loudness response curve to a stimulus of 40 decibels.

The methods I have so far described are applicable in evaluating frequencies in the sonic range. The problem becomes more involved when we try to measure and analyse frequencies in the ultrasonic field. Equipment is complicated and the design and calibration of a microphone in air for this purpose presents many difficulties.

Ultrasonic frequencies, i.e. those above 20,000 c.p.s. have a short wave length, form relatively sharp sound shadows, can be focused to give intense local pressures and are attenuated more readily as they travel through air.

For the last few years we have been engaged in developing equipment which will not only record the presence of ultrasonic radiation in air, but will also analyse the radiation in terms of frequency and intensity.

## Some Characteristics of the Ear

The ear is very sensitive to very small variations of pressure in the air, and it can also tolerate very large ones. The ear responds approximately logarithmically to sound; thus if two sounds of equal intensity are present at the same time, the resulting sensation of loudness is more nearly equal to the logarithmic rather than the arithmetical sum of the combined intensities.

The sensation of loudness is a complex phenomenon for it depends on the frequency and intensity level of the sound. The ear responds in such a way that two tones of the same intensity but of different frequencies do not necessarily appear equally loud. If two equally loud tones of different frequencies are increased in intensity by equal amounts there is usually an unequal increase in the sensation of loudness. Thus an 80 c.p.s. sound with an intensity level of 60 decibels seems as loud as one of 6,000 c.p.s. at 40 decibels or one at 1,000 c.p.s. at 30 decibels.

The ear is much less sensitive at low intensity levels to low-frequency tones than to those of 500 to 5,000 c.p.s. Above 90 decibels intensity the sensitivity of the ear is fairly constant over the entire frequency range.

The difficulty of hearing a given sound or understanding speech in a background of noise is due to the masking effect of such noise. It becomes necessary to raise the intensity of such a sound or word to make it audible and this increase of the threshold intensity in decibels represents the degree to which it is masked by the ambient noise.

Table I, which shows relationship levels of noise of certain intensity, will give a better idea of the magnitude of the noise around us in our everyday life.

TABLE I

| Conversation level | Noise level in decibels | Air or land travel | Interior building | Outdoor environment |
|---|---|---|---|---|
| Impossible .. | 115–130 | Pilot's compartment in modern combat aircraft | — | Riveter |
| Shout .. | 100–110 | Interior of aircraft. Underground railway | Proximity to aeroplane engine. Boiler shop | Pneumatic drill |
| Very difficult | 80–95 | Sports car .. .. .. | Loud indoor radio | Very heavy traffic |
| Raised voice | 60–75 | Railway sleeper .. .. | Noisy restaurant. Department of large store | Brisk traffic |
| Normal .. | 35–55 | Quiet motor car .. .. | Noise on a busy street with windows open. Quiet office | Quiet street |
| Whisper .. | 0–30 | — | Quiet residence. Studio for filming | A quiet garden in a London square |

It can thus be seen that noise is our almost constant companion. Indeed exposure to excessive noise is considered part of the price modern man pays for his civilization. With the progress of mechanization, noise levels have increased and impairment of auditory acuity occurs.

### Effects of Intense Sound and Ultrasound on Auditory Functions

The relationship between exposure to intense noise and loss of hearing has been known for over one hundred years. Fosbrooke in 1831 called attention to the frequent occurrence of deafness among blacksmiths while Barr in 1896 established noise as the cause of deafness in boiler-makers. Later it was found that other workers in noisy surroundings suffered a more or less typical hearing loss.

The term "acoustic trauma" has been given to the resultant effects whether temporary or permanent following exposure to noise. There are certain factors which, because they influence the degree of hearing loss resulting from acoustic trauma, must be considered. These can be summarized as follows: (1) total time of exposure; (2) length of exposure per period; (3) loudness or intensity of the stimulus; (4) character of the sound stimulus, whether continuous or interrupted; (5) frequency characteristics of the noise; (6) type of environment; (7) whether any protective devices have been used; (8) the age of the individual exposed (older persons probably are more susceptible and have less recuperative power); (9) history of any previous aural disease; (10) constitutional factors such as differences in sensitivity.

Noise exceeding in intensity a level of 90 decibels is responsible for acoustic trauma. Whether the noise originates in the boiler-maker's shop or in the test bed of an aeroplane engine the earliest manifestation of the insult inflicted on the aural mechanism is an abrupt dip or gap in the hearing ranges as determined by the audiometer near 4,096 c.p.s. I must emphasize that individuals with this loss at first give no indication that their auditory acuity is impaired. This hearing loss which involves the clarity of speech more than the apparent loudness is not an uncommon occurrence. Errors in hearing what is said are certain to occur occasionally in daily life, but they either pass unnoticed or are attributed by the listener to incoherency on the part of the speaker.

The types of acoustic trauma have been classified by certain observers into (*a*) Explosive type and (*b*) Chronic noise deafness.

In the explosive type the trauma follows acute concussion of the inner ear which damages the cochlea and produces profound and permanent nerve deafness. Losses may occur at all frequencies but more often at high ones. Trauma may arise from any sudden very loud noise which occurs close to the unprotected ear. The loss may be immediate and may be permanent.

In the chronic type, deafness follows insults from long-continued exposure to loud noise. Sounds of high frequency produce greater acoustic trauma than those of low frequency.

The traumatizing effect from interrupted sharp sounds is greater than that from a continuous sound of similar frequency, intensity and duration.

Interrupted sounds cause more trauma than constant sounds. We can compare them to interrupted tactile stimuli which are more annoying than constant touch or to blinking lights which are more disturbing than lights of constant intensity.

Usually the greatest hearing loss occurs at a frequency about half an octave above the exposure tone and no significant raising of the auditory threshold is produced for tones of frequency lower than the exposure tone.

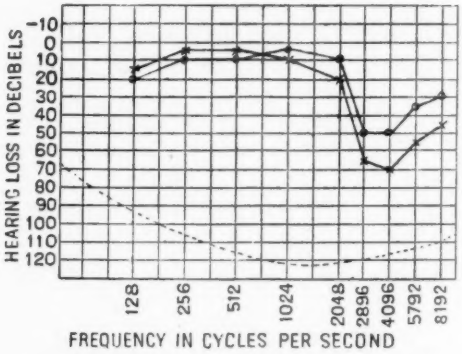
With longer exposures the hearing loss may be quite extensive for all tones above the exposure frequency.

If we take as a measure of hearing loss the average loss through the two octaves above the exposure tone we find that:

(1) 1,000 and 2,000 c.p.s. are about equally effective in producing hearing loss.
(2) 4,000 c.p.s. is much more effective and 500 c.p.s. is much less effective than 1,000 or 2,000 c.p.s.
(3) Hearing loss develops most rapidly during the first minutes of exposure and then more and more slowly.
(4) Recovery of hearing usually begins rapidly and progresses more and more slowly; it tends to be lowest for frequencies at about 4,000 c.p.s., regardless of the frequency of the original exposure tone.

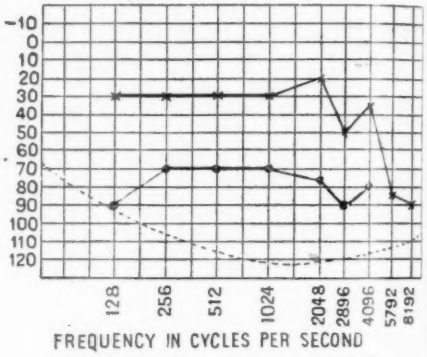
If the hearing loss is of the order of 60 decibels it may take four or five days for hearing to return to its normal level. Some people are much more susceptible than others to the production of hearing loss; likewise the rate of recovery from a given degree of loss may vary (Figs. 2 A and B and 3 A and B).

We carried out an investigation to ascertain whether auditory deterioration sets in during training of flying personnel and at what stage it becomes apparent, i.e. after how many hours' flying. The most noticeable factor arising out of the inquiry was that pilots flying multi-engined aircraft are more prone to show a loss of auditory acuity than single-engine pilots. This results from the relative position of the pilot to the engines.



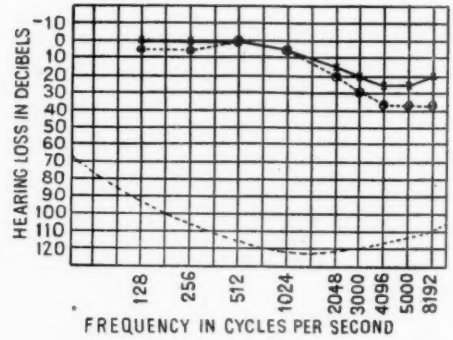

AIR CONDUCTION: RIGHT O, LEFT X

FIG. 2A.—Audiogram of a member of gun crew knocked down by blast of detonator from 5-in. gun. Cotton-wool plugs loosely worn. Tinnitus ++. No change in hearing after one year.



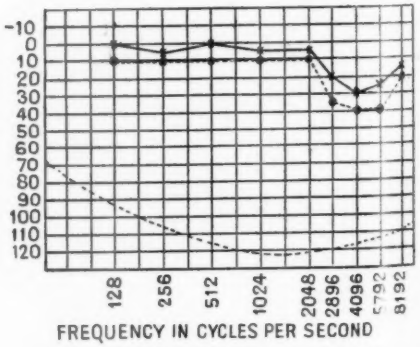

AIR CONDUCTION: RIGHT O, LEFT X

FIG. 2B.—Audiogram of a man whose right ear was exposed to one single round of fire from a 90 mm. gun located at 10 ft. to his right. He experienced pain in his right ear. Deaf in both ears immediately following exposure. Hearing returned in left ear after two months, but right ear was still deaf when examined eighteen months after. Tinnitus ++ has persisted.




AIR CONDUCTION: RIGHT O, LEFT X

FIG. 3A.—Audiogram of a riveter showing acoustic trauma, confined to high tones. Rinne positive right and left. Weber not lateralized.




AIR CONDUCTION: RIGHT O, LEFT X

FIG. 3B.—Audiogram of a riveter in an aeroplane factory—a typical graph of acoustic trauma. A year ago his audiogram was normal. His Rinne is positive in both ears, and Weber is not lateralized.

The highest recordable loss for twin-engined pilots at 8,192 c.p.s. was 25 decibels, the lowest 5 decibels. The highest for 4,096 c.p.s. was 35 decibels.

The onset of a measurable loss restricted to high tones becomes apparent at an early stage when it is probably recoverable. The earliest time at which any loss measurable by audiometry showed itself is after an average flying time of approximately 80–100 hours. A loss was found at 4,096 and 8,192 c.p.s. and this is in agreement with our previous observations.

Campbell and Hargreaves (1940) studied airmen and found that the first inflexion of the normal

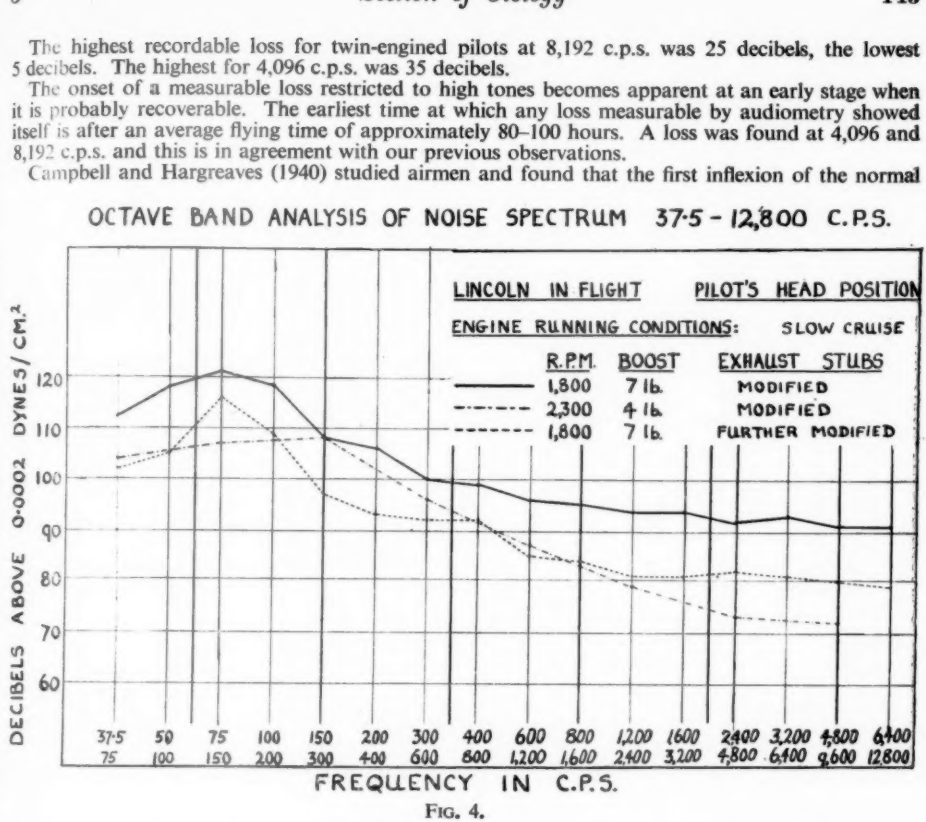
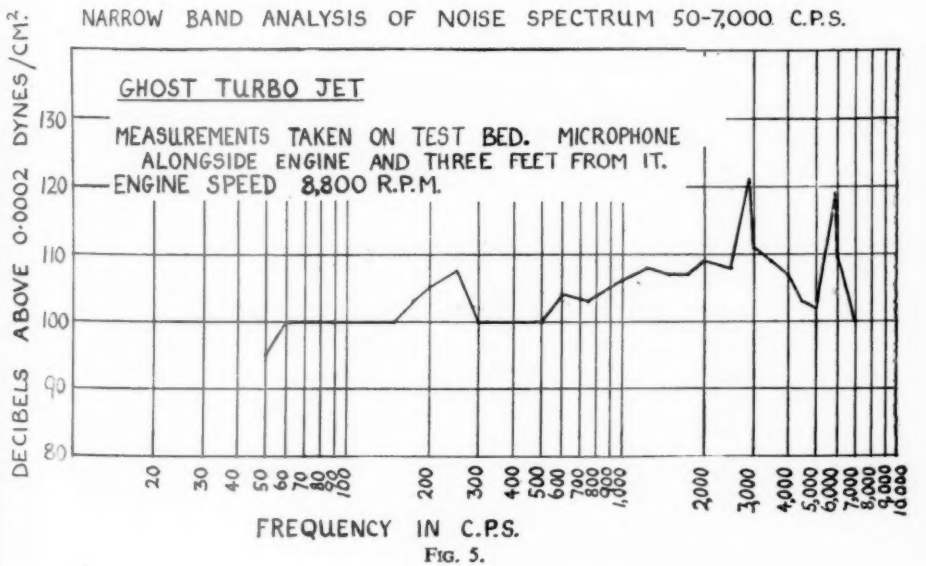

OCTAVE BAND ANALYSIS OF NOISE SPECTRUM 37·5 - 12,800 C.P.S.
LINCOLN IN FLIGHT
PILOT'S HEAD POSITION
ENGINE RUNNING CONDITIONS: SLOW CRUISE
R.P.M. BOOST EXHAUST STUBS
1,800 7 lb. MODIFIED
2,300 4 lb. MODIFIED
1,800 7 lb. FURTHER MODIFIED
DECIBELS ABOVE 0·0002 DYNES/CM.²
120
110
100
90
80
70
60
37·5 50 75 100 150 200 300 400 600 800 1,200 1,600 2,400 3,200 4,800 6,400
75 100 150 200 300 400 600 800 1,200 1,600 2,400 3,200 4,800 6,400 9,600 12,800
FREQUENCY IN C.P.S.

FIG. 4.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GHOST TURBO JET
MEASUREMENTS TAKEN ON TEST BED. MICROPHONE ALONGSIDE ENGINE AND THREE FEET FROM IT.
ENGINE SPEED 8,800 R.P.M.
DECIBELS ABOVE 0·0002 DYNES/CM.²
130
120
110
100
90
80
20 30 40 50 60 70 80 90 100 200 300 400 500 600 700 800 900 1,000 2,000 3,000 4,000 5,000 6,000 7,000 8,000 9,000 10,000
FREQUENCY IN C.P.S.

FIG. 5.

curve appeared at 4,096 c.p.s.; with more severe loss, however, the adjacent frequencies 2,896 and 5,792 were affected to an almost equal degree.

Grow and Armstrong stated that an aviator who is repeatedly subjected to noise of 80 to 90 decibels of intensity, or above, will usually show some loss of hearing after a period of years.

We demonstrated in 1939 the occurrence of the early loss in aviators and expressed the view that the auditory defect was probably progressive in character, if exposure to intense noise was continuous. We reproduced the dip or gap by exposing our unprotected ears to very loud aeroplane noise during flights in multi-engined aircraft. Whereas in piston-engined aircraft low and middle sonic frequencies predominate (Fig. 4), in jet-propelled aircraft the principal features in the corresponding spectrum are high sonic frequencies (Fig. 5).

Personal exposure to jet-engined sound of approximately 145 decibels intensity enabled us to determine the rate of recovery which followed such exposures. The maximum energy output occurred in the region of 2,000 c.p.s. Two exposures to the noise with ears unprotected were carried out (Tables II and III).

TABLE II.—SUBJECT "A"

Time of exposure 35 minutes. 30 feet from source and facing it.

Audiogram taken ten minutes after exposure

| Right ear | | | | Left ear | | |
|---|---|---|---|---|---|---|
| Difference | After | Before | Frequency | Before | After | Difference |
| 35 | 40 | 5 | 8,192 | 0 | 25 | 25 |
| 70 | 70 | 0 | 4,096 | 0 | 65 | 65 |
| 60 | 60 | 0 | 2,048 | 5 | 65 | 60 |
| 20 | 25 | 5 | 1,024 | 5 | 20 | 15 |
| 10 | 20 | 10 | 512 | 5 | 20 | 15 |
| 5 | 20 | 15 | 256 | 10 | 25 | 15 |
| 10 | 25 | 15 | 128 | 15 | 25 | 10 |

Marked tinnitus with severe degree of hearing loss to conversation voice resulted.
Complete recovery thirty-six hours after exposure.

TABLE III

Time of exposure 30 minutes. 15 minutes with right ear towards source of sound and 15 minutes with the left ear. Distance 15 feet from source

| Right ear | | | | | | | | Frequency | Left ear | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 5 | 10 | 40 | 35 | 45 | 45 | 65 | 0 | 8,192 | 0 | 55 | 45 | 45 | 40 | 25 | 10 | 5 |
| 5 | 5 | 30 | 30 | 85 | 50 | 65 | 0 | 4,096 | 0 | 65 | 50 | 60 | 50 | 40 | 15 | 0 |
| 10 | 5 | 10 | 10 | 25 | 20 | 35 | 0 | 2,048 | 0 | 45 | 35 | 30 | 25 | 20 | 5 | 0 |
| 5 | 5 | 5 | 0 | 10 | 15 | 25 | 0 | 1,024 | 0 | 30 | 30 | 20 | 20 | 15 | 5 | 0 |
| 5 | 5 | 5 | 10 | 5 | 15 | 15 | 5 | 512 | 5 | 15 | 5 | 0 | 5 | 5 | 0 | 0 |
| 10 | 5 | 10 | 15 | 10 | 15 | 15 | 10 | 256 | 10 | 20 | 10 | 0 | 15 | 15 | 5 | 5 |
| 5 | 0 | 5 | 15 | 10 | 10 | 15 | 10 | 128 | 15 | 20 | 10 | 5 | 15 | 15 | 10 | 5 |

1—Audiogram taken before exposure
2—Audiogram taken 10 minutes after exposure
3—Audiogram taken 1½ hours after exposure
4—Audiogram taken 6 hours after exposure
5—Audiogram taken 21½ hours after exposure
6—Audiogram taken 26 hours after exposure
7—Audiogram taken 70 hours after exposure
8—Audiogram taken 146 hours after exposure

It will be seen that maximum hearing loss is approximately an octave above the peak frequency of about 2,000 c.p.s.

The impairment of hearing produced by exposure to loud tones or noise is of the perceptive type. Though the threshold may be elevated 50 or 60 decibels there may be little or no loudness loss for sounds at 100 decibels loudness level. An audiogram alone, however, is not an adequate measure of the impairment of auditory function. The impairment of understanding speech is more closely related to the overall loudness loss at the intensity level at which speech is heard than to the threshold audiogram or to the loudness loss in any special portion of the speech frequency range (400–4,000 c.p.s.).

Prolonged exposure to noise of wide frequency spectrum causes severe articulation loss at a low loudness level (i.e. 40 decibels) but only moderate loss at a high level (100 decibels).

There is no evidence at present that ultrasound has any effect on auditory function.

Nor is there evidence that any of the nerve endings in the body are capable of informing the individual of the presence of ultrasonic radiation. We have little or no knowledge of the effects of ultrasonic vibrations on the human body and there is no evidence that airborne ultrasonics can produce any specific direct effect on the brain or other parts of the nervous system. In the realm of physics most of the work has been done in liquids but little is known of the range, propagation and transmission of ultrasonic vibrations in gases. Their biological effects seem to be related to the enormous alternating local pressures which are produced in the tissues and to the local heating effects arising from the absorption of energy in dampening the vibrations. Very small organisms and red blood corpuscles can be destroyed.

Ultrasonics can be easily reflected by the human skin. In contrast, a furred animal absorbs a greater proportion of sound energy, something like 12%. This energy is turned into heat which may be sufficient to kill a small animal like a rat or mouse. Intensities of 160 decibels can do this. Guinea-pigs and mice exposed to a frequency of 30,000 c.p.s. at an intensity of 150–155 decibels have succumbed as a result of rise of body temperature. In man the absorption coefficient decreases rapidly with increasing frequency.

Certain claims have been made by German investigators into the beneficial effect of ultrasonics on certain forms of cancer and neuritis.

We do not know yet how much margin of safety there may be between any beneficial effects on diseased tissue and injurious effects on surrounding normal tissue.

In this field of work contact between the crystal generator and the exposed material was made through an oil or water medium from which air had been carefully excluded. Under these conditions surface reflection phenomena are minimal and nearly all the sound energy generated by the crystal is absorbed in the exposed biological material, thereby heating or otherwise destroying the structure. Much of the confusion concerning ultrasound as a hazard arises from the mistaken inference that the results obtained with fluid coupled generators are valid for airborne frequencies.

### Pathological Changes Resulting from Intense Sound and Ultrasound

We have very little evidence of the pathological changes which occur in the human cochlea when exposed to noise or frequencies of high intensity. Lurie, Davis and Hawkins (1944) have carried out animal experiments and their findings deserve careful study.

They exposed guinea-pigs to pure tones of various frequencies at intensities from 140 to 145 decibels. It was found that the least detectable anatomical damage to the organ of Corti was the disappearance of the mesothelial cells in a limited area from the scala tympani surface of the basilar membrane. This was produced by a frequency of 1,000 c.p.s. at 140 decibels for three minutes. Severe and extensive damage is produced by more intense tones and by longer exposures.

The damage produced by intense tones consists of degenerative changes with rupture and dislocation of the organ of Corti from the basilar membrane. A few days or weeks after exposure to intense tones the organ of Corti disappears when it has been severely damaged and the nerve fibres and the ganglion cells begin to degenerate.

Mild degrees of damage are localized but severe exposure, say of 150 decibels for several minutes, cause widespread damage to the organ of Corti. Furthermore the damage tends to locate nearer the helicotrema when caused by low tones but nearer the round window when caused by high tones.

Once the organ of Corti has been damaged and degeneration of cells is present, there is no subsequent regeneration. The final result is complete absorption of the damaged cells with an accompanying degeneration of the nerve fibres and ganglion cells leading from the site of the lesions. It is possible to cause severe and extensive damage to the organ of Corti by loud tones without apparent injury to the ear drum or ossicles.

During the last war I observed, when the tympanic membrane had been ruptured as the result of a high explosive blast, that the auditory acuity showed less impairment than when the membrane was intact. Presumably the energy expended in rupturing the membrane was not transmitted to the inner ear with the same force.

Alexander and Githler (1949) measured the cochlear potential at various intervals for four groups of guinea-pigs after a fifteen minutes' exposure to jet-engine noise. A control group was also tested. They found:

(1) Auditory impairment throughout the frequency range.
(2) Partial recovery occurs progressively up to three weeks following exposure.
(3) After injury the cochlear potentials are further impaired on the presentation of even moderately intense sounds. The exposed ear has been rendered unusually susceptible to further injury.
(4) Preliminary evidence indicates the possibility that further degeneration occurs between three and six weeks after the stimulation.
(5) Protected ears show no immediate effects in auditory acuity.

It is interesting to find some support for an impression I have formed as a result of observations into the problem for many years, viz. that auditory damage, once produced, lowers the threshold of susceptibility to further damage. This may help to explain the puzzling nature of the progressive auditory impairment we so often find clinically.

Davis, Parrack and Eldredge (1949) report what they believe to be the first case of rupture of the human ear drum under experimental conditions by exposure to a sustained sound of measured intensity. The frequency was 6,500 cycles per second, the exposure lasted for five minutes and the intensity varied from 156 to 164 decibels depending on the position of the subject's head in the sound field.

When the subject first placed his head in the sound field the pain was so intense that he was forced to withdraw his head for a few moments (pain becomes apparent in the region of 120–130 decibels). He nevertheless held his head in the sound field at the limit of pain he could tolerate. He describes it as "not the ordinary sharp pain from sounds above 145 decibels, but a new kind that included

dull as well as sharp pain". At the end of the exposure there was blood in his external auditory meatus and otological examination showed a small rupture near the centre of the drum. The hearing in this ear was depressed above 1,000 cycles per second and was immeasurable above 8,000 c.p.s. The drumhead healed well and normal hearing for most frequencies returned within a few days, but the loss for high tones above 9,000 c.p.s. remained.

### Effects of Intense Sound and Ultrasound on Vestibular Function

We have recently reported some observations on this subject (Dickson and Chadwick, 1951). The advent of the turbo-jet engine focused attention on certain subjective sensations which occurred infrequently and erratically. Many injudicious Press reports have appeared from time to time based on scanty knowledge of possible harmful effects resulting from ultrasonic frequencies generated by jet aircraft. This no doubt makes sensational reading, but it has led to a number of purely psychological disturbances being experienced, not only by jet personnel but by other people not even remotely connected with the jet engine.

A transient vestibular irritation induced by standing in close proximity to turbo-jet engines when run at certain speeds has been experienced by many observers. It is unlikely that this phenomenon is due to the presence of ultrasonic waves as was at first suggested. It is well known that stimulation of the vestibule can be caused by sufficiently loud acoustic stimuli.

Frequency analyses have shown that sounds within the normal range of audibility can be generated by jet engines at such sufficiently high intensities that an adequate stimulus to the labyrinth is provided in normal individuals. (Some reports indicate that frequencies above the normal sound range can also produce similar effects.)

Ultrasonic spectra so far have revealed that during the test-bed running of jet engines, frequencies above the range of audible sound are of so low an intensity as to be thought incapable of causing deleterious results.

Inquiries revealed that no symptoms of consequence have been experienced during flight by any of the personnel questioned. Such symptoms of dizziness and unsteadiness occurred only among ground staff during running-up of engines in the test bed or on the airfield.

Personal exposure at certain positions in relation to the air intake and at certain engine speeds produced momentary sensations of imbalance which were accentuated by rapid acceleration and deceleration of the engine. The sensation was experienced within an arc between 30 degrees to 40 degrees to the axis of the intake and two yards away from it. It is a disturbing feeling of general instability and weakness with a peculiarly unpleasant reverberation passing through the head. No nystagmus was observed in those actually feeling unsteady, though nausea was reported in some instances following the exposure. On the particular engines on which our investigations have been carried out the speeds ranged from 5,000 to 7,000 revolutions per minute, where the recorded intensities at frequencies between 1,600 c.p.s. and 4,400 c.p.s. were between 120 and 130 decibels when analysed. Blocking the external auditory meatus with a finger immediately abolished the symptoms of unsteadiness. At the moment we have no grounds to suppose ultrasonic frequencies are mainly responsible for these symptoms. The effects are largely due to high intensities and not to high frequencies as such.

Hallowell Davis (1948) in his survey of the biological and psychological effects of ultrasonics stresses the importance of what he terms "sonic ultra-intensities". In a publication of 1949 he and his co-workers place emphasis on the intensity scale being of more importance than the frequency scale when considering the hazards of sound and ultrasound.

The possibility of the peripheral part of the vestibular apparatus being stimulated by the intense noise generated has been considered, though objections to this idea can be raised because no nystagmus was observed.

The absence of a sensation of rotation has suggested the possibility of the utricle being the area stimulated. Another possible explanation may be a central overflow of auditory impulses to neighbouring nuclei.

We have no grounds for supposing that ultrasonic frequencies are responsible for any vestibular symptoms. Recently Vyslonzil (1949) has, however, demonstrated that in guinea-pigs exposure of the labyrinth to ultrasonic waves resulted in nystagmus to the side which was exposed.

It has been shown experimentally that the enormous pressure differences between the crest and trough of an ultrasonic vibration can produce the condition known as cavitation. Cavities and hollows are formed which tend to fill with sub-microscopic bubbles arising from gases dissolved in surrounding liquids. It is believed that the formation of such bubbles in the tissue is mainly responsible for the damaging effect of ultrasonics.

It is possible that ultrasonic frequencies of high intensity may cause the formation of bubbles in the endolymph although this supposition is purely conjectural.

Huizinga, however, has found that by introducing bubbles in the semicircular canal fistula of his experimental animals the Tullio reaction remained positive, even though the fistula was blocked by wax. A fistula occluded without the presence of an air bubble caused the reaction to disappear.

### Noise as an Industrial Problem

As an industrial problem intense noise has not received the attention it merits, because it is by-passed by managements who do not clearly realize the possibility of increased efficiency and production through curtailment of noise.

Several other factors have also been responsible for the failure to recognize noise as a problem; among them are:

(*a*) Ambiguity both in the understanding of what constitutes loss of useful hearing and the way it should be measured.

(*b*) The relatively recent development and standardization of satisfactory instruments for measuring hearing loss.

(*c*) The attitude on the part of many that the problem is better left alone since to investigate the hazards of noise would merely emphasize and invite attention to a condition which has never been properly defined.

(*d*) A reluctance on the part of employees to complain of any symptoms for fear it will bring about loss or limitation of employment.

(*e*) The question of compensation for loss of hearing from exposure to industrial noise.

We must appreciate that a potential problem does exist and that deafness can and will result from high noise levels in industry and elsewhere. Various causes of deafness can be found in a random selected group of deaf people—such conditions as respiratory infection, pressure changes, normal deterioration with age and possibly also the additional variables of race and sex. This spate of causes only helps to complicate the interpretation of deafness.

Some losses of hearing, however, have similar and relative constant characteristics. In certain occupations associated with continual exposure to loud noise there is no doubt that deafness results which with long exposure is progressive, and may be permanent. The worker's deafness (because of its innocuous origin in the little used high-frequency range) neither stimulates executive interest nor the interest of the worker himself, as does a temporary injury such as a broken arm, with which the relationship between cause and effect is more evident.

It is doubtful whether complete immunity from the inimical effects of excessive noise can ever be acquired so long as normal hearing is retained; the development of partial deafness appears to be the only effective protection which the individual can acquire. It is probable that in the psychological sense tolerance to noise can be established in some measure. It may be possible to become acclimatized so that consciousness of the subjective effects such as irritation and annoyance ceases or becomes less acute. Some of the effects, however, remain and are revealed only by objective measurements.

The obvious and direct safeguard is to reduce the noise level in the working environment. We do know that levels of 100 decibels and above will produce fatigue and deafness and that levels of 80 to 90 decibels are annoying.

We have evidence that continued exposure to noise levels of the order of 80 to 90 decibels for long periods may lead to the acceleration of the normal deterioration in hearing with age. Noise, whatever its origin, does damage hearing, and therefore all persons exposed to intense noise should use some form of protective device such as helmet or ear warden. Workers will not wear a protective device because it can be very uncomfortable unless care is taken in the individual fitting. Weiss (1946) comments that objection to the use of ear plugs by gunners on the basis of inability to hear commands and signals is not valid because the loud spoken voice actually is heard better in a noisy environment when an ear warden is in place, than when the ears are unguarded. The plug eliminates excessive extraneous noise.

In a reverberant space the worker has the sensation of working at a noisy machine in a noisy environment. But when reflecting surfaces such as high reflecting walls and ceiling surfaces are replaced by absorbing surfaces the environmental factor is reduced thus mitigating the annoyance, even though the measured noise level is not markedly decreased. A non-absorbent surface, e.g. a steel plate, reflects as much as 80 to 90% of the sound energy striking it. Consideration must be given to the spreading effect of sound. In an open space the intensity of sound from a given source falls off rapidly as the distance increases. In a reverberant room the sound intensity from a single source is almost independent of the distance from the source and the sound spreads with little diminution.

The planning and layout to reduce factory noise should receive more attention. Isolation of heavy machines by means of effective shock mounting will reduce building vibrations which are transmitted throughout steel and concrete structures. The design of aeroplane test benches has shown what can be done in protecting workers from the effects of intense noise. Observation cabins, properly insulated, house the necessary instruments, gauges and equipment. There the worker is exposed to a noise level of probably 80 to 90 decibels instead of 130 decibels on the actual engine bed.

In addition to modifying the working environment and controlling noise at the source certain other measures should be taken which mainly concern the individual.

All personnel exposed to an intensity of noise above 90 decibels should be examined audiometrically before engagement and thereafter at stated intervals. It is important, however, that the testing conditions and equipment should be standardized.

We require data on the capacities of hearing of the individual prior to employment and his auditory progress whilst employed.

Repeated surveys of the most exposed groups are indicated, accompanied by the study of the magnitude and spectrum of the noise at various places in the occupation. We must institute systematic studies of sound levels in noisy industries; for the increment of injury contributed by the occupation can only be evaluated in large groups of men in relation to measured noise levels.

Personnel working in noisy surroundings should be educated on the significance of protection against intense noise.

It should also be realized that there is a great range of magnitude in susceptibility. This suggests screening new employees for susceptibility to noise. No reports appear to be available on this point the test should be arranged.

If preventive action against the noise hazard in industry is to be initiated and success in its application be realized, certain fundamental measures must be taken.

Finally, when one considers those dwelling places with thin, cheaply built walls and floors which act as insignificant barriers to the passage of sound we realize what little attention has been directed to the problem of noise. Insulation can be obtained, but it should be cheap enough to be used in all houses. Only when we become aware that quiet living conditions are essential to the health and maximum efficiency of the individual will the question of noise receive the attention it deserves in the planning of homes.

## Summary

Noise can impair hearing by its intensity as well as by its duration. The intensity scale of sound is of more importance than the frequency scale when considering the hazards of sound. The intensity has been considered the most important factor in the causation of vestibular disturbance.

We have no evidence at present to indicate that airborne ultrasonic vibrations constitute a hazard to hearing. Our experimental, though limited, work in this field has so far been negative.

Impairment of hearing can be gradual in development with the high tones being affected first; while the loss is at first reversible, prolonged exposure leads to irreversible changes.

Every endeavour should be made to limit noise by considered distribution of machinery, sound proofing, bedding of equipment and particularly by protection of the ears. Resulting deafness in noisy occupations should be termed an occupational hazard and people in such occupations should have their hearing checked periodically.

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# Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*November* 25, 1952]

## DISCUSSION: TREATMENT OF NON-TUBERCULOUS MENINGITIS [*Abridged*]

**Dr. H. Stanley Banks:**

The treatment of non-tuberculous meningitis depends on certain basic points:

*Basic pathology.*—The basic lesion in meningococcal cases (and probably in other bacterial meningitis) seems to be an endarteritis or endangiitis which permits local proliferation of the organisms. This is suggested by histological findings of small vessels stuffed with meningococci in the petechiæ of the skin and in the adrenal cortex (Banks, 1951). Such lesions could lead to thrombosis, infarction, ischæmia, and penetration of the blood-brain barrier. In addition to meningitis the following metastases may be produced in different cases—subdural hæmorrhage and fluid collections; diffuse and focal cerebral hæmorrhages, perivascular infiltrations and abscesses; suprarenal hæmorrhage and cortical cell degenerations; pituitary focal necrosis; pericarditis; pleural and synovial effusions; hepatitis; choroiditis; labyrinthitis, &c. (Banks, 1948). In cases of fulminating septicæmia, however, part of the damage, particularly the adrenal cortical cell degeneration and exhaustion, may be a direct effect of the stress of the overwhelming toxæmia.

*Subdural hæmorrhage and fluid collections.*—The subdural metastasis has recently been recognized to an increasing extent. In 1942 I described a fatal meningococcal case which caused cerebral compression with a clinical picture indistinguishable from the "encephalitic" type. Honor Smith, while making burr holes in a case of pneumococcal meningitis found a large collection of yellow subdural fluid (Smith *et al.*, 1946). In 1950, McKay *et al.* found xanthochromic or cloudy sterile subdural fluid in 9 out of 23 cases of *H. influenzæ* meningitis. In 1952, Jones found 6 subdural effusions in cases of purulent meningitis due to various organisms including *B. coli.* Such subdural fluid in treated cases is usually hæmorrhagic or xanthochromic and sterile; only rarely is it encapsulated pus. Suggestive symptoms are continued mild fever, bulging fontanelle, vomiting or convulsions after apparently adequate therapy. The smaller fluid collections are doubtless often absorbed undiagnosed. The larger may require needling through the fontanelle or coronal suture, or surgical exploration.

*Need for early diagnosis.*—Success in treatment depends on this so much that in any acute case immediate lumbar puncture is indicated for the slightest degree of neck stiffness and inability to kiss the knees. In infants, neck stiffness is easily missed and Kernig's sign is negative. In the first month or so of life refusal to feed and mild fever may be the only signs. In adults the mild cases are the most difficult to diagnose. Awareness of minimal meningeal signs is the pre-requisite for success.

*Need for optimal therapy.*—Chemotherapy should be sharp and short. There is no place for timid dosage. Drug toxicity is a secondary consideration. The most suitable drug for the suspected organism is given at once in maximum dosage, and the pathologist is asked to determine the sensitivity of any organism isolated to the various antibiotics. This is essential except for the meningococcus, since different strains within most bacterial species vary so much in their sensitivities. It is particularly necessary for staphylococcus, *B. coli*, salmonellæ, proteus, *B. pyocyaneus*, and all organisms of low pathogenicity. An adjuvant drug should be used whenever there is doubt as to sensitivity to the principal drug.

*Disadvantages of intrathecal therapy.*—Thecal hæmorrhage, fibrosis and secondary infection are far from negligible risks in practice, and meningeal irritation and delayed resolution are inevitable accompaniments. Advantage should be taken of the increased permeability of the meninges in acute meningitis, and systemic therapy alone employed whenever it is sufficient. At present this applies only to sulphonamide and chloramphenicol in ordinary doses and to penicillin in enormous doses, e.g. 1 million units intramuscularly two-hourly. The latter produce bactericidal concentrations in the spinal fluid. Streptomycin penetrates poorly and must be used intrathecally. Penetration with Aureomycin is irregular and may be delayed up to forty-eight hours, and with Terramycin it is practically nil.

DRUG CONCENTRATIONS IN SPINAL FLUID PER CENT OF BLOOD LEVELS IN ACUTE MENINGITIS

| | |
|---|---|
| *Sulphadiazine* | *50–70* |
| Sulphathiazole | 15–40 |
| Penicillin, ordinary doses | trace |
| Streptomycin | 10–20 |
| *Chloramphenicol* | *30–50* |
| Aureomycin | Irregular: delayed |
| Terramycin | trace |
| *Penicillin, 1 million units two-hourly* | *0·05–0·5 unit/ml.* |

### *Meningococcal Meningitis*

Meningococci still show no significant resistance to the more powerful sulphonamides, and for the ordinary form of the disease no adjuvant drug is required. A single injection of not more than 20,000 units of penicillin may be given intrathecally if the first lumbar puncture yields turbid or purulent fluid and if clinical evidence is against the probability of meningococcal infection. Intrathecal injection is undesirable, however, if there is a petechial rash or other likely evidence of meningococcal disease. Although it is usually harmless, its irritant effect may keep cell and protein content of the fluid above normal for weeks or even months. Dosage of sulphonamide must be maximal. No infant, for example, should have less than 3 grammes daily for the first three or four days. Mortality from meningococcal disease is still surprisingly high. Year after year the Ministry of Health reports a fatality rate of 24 to 30% of *notified cases*. The highest incidence and the highest death-rate are in the first year of life. So with morbidity. Wolff (1952) followed up a series of cases in Birmingham some ten years after the attack and found far more mental deterioration (as judged by I.Q. tests) and far more deafness (as shown by audiometer tests) resulting from an attack under the age of 1 year than at later ages in childhood. The still formidable mortality and morbidity of this disease require for their reduction earlier diagnosis and more vigorous treatment, especially in infancy.

In fulminating septicæmia, systemic penicillin should be given as well as sulphonamides. If peripheral circulatory collapse is demonstrated, a few doses of cortisone 50–100 mg. may be life-saving. If cortisone is not available a useful substitute is adrenal cortical extract in heroic dosage, e.g. 20–40 c.c. i.v. followed by 10 c.c. hourly for six hours and then three-hourly for some days (Faloon *et al.*, 1950). If possible, adrenal replacement therapy should be controlled by the eosinophil count which should be kept below 15 per c.mm. The rare encephalitic cases with deep coma and signs of intracranial pressure should have frequent injections of 50% glucose i.v. On rare occasions I have seen this restore consciousness temporarily, and after repeated injections completely; but it often fails.

### *Pneumococcal Meningitis*

My personal experience of this disease is not large and has been mostly confined to relatively favourable age groups. In these I have had remarkable success with the standard method of treatment —systemic penicillin 200,000 to 500,000 units four-hourly and intrathecal penicillin 20,000 units daily for four or five days, with sulphadiazine orally added as an adjuvant. Recoveries have been just a little slower than in meningococcal meningitis. But Lepper and Dowling (1951) state that approximately one-third of the cases in large unselected series in U.S.A. still die. The fatal cases mainly comprise those comatose or moribund on admission, those who die within forty-eight hours of the start of the treatment and very old persons suffering from intercurrent disease. It seems unlikely that much improvement can be effected in such groups. Yet it is claimed by Dowling *et al.* (1949), Lepper and Dowling (1951) and Bunn and Peabody (1952) that massive systemic penicillin (1 million units two-hourly) without intrathecal treatment gives improved results when compared with controls under "standard" treatment. It is certainly an advantage to eliminate intrathecal treatment but disadvantages are the expense and the disturbance of the patient by two-hourly injections. The massive penicillin regime might be recommended for unfavourable cases but seems hardly necessary for the younger and more favourable cases. A later improvement in the method is to give one intrathecal injection at the outset since a bactericidal concentration in the spinal fluid may not be reached for eight hours.

The combination of penicillin and Aureomycin has given definitely worse results than penicillin alone (Lepper and Dowling, 1951). I am surprised that chloramphenicol alone does not seem to have been tried in a big way in pneumococcal meningitis. I think it might prove to be as effective as penicillin, but we must wait for evidence.

The primary focus, if identified, in ears, sinuses, lungs, joints or elsewhere, may require special surgical or other treatment.

### *Hæmolytic Streptococcal and Staphylococcal Meningitis*

Specific treatment in these forms is similar to that of pneumococcal meningitis except when the staphylococcus is penicillin-resistant. In that case I would use chloramphenicol and sulphadiazine systematically.

### Streptococcus Viridans *Meningitis*

My one case occurred in 1943–1944. It was one of the first brilliant successes of penicillin after a slow losing battle had been fought with sulphonamides over a period of four months. Most cases are associated with subacute bacterial endocarditis or with nasopharyngeal, sinusal or dental foci. Some strains are relatively insensitive to penicillin and require massive dosage.

### Hæmophilus Influenzæ *Meningitis*

This infection seems to be invariably due to Pittman type b *H. influenzæ*, and formerly was 100% fatal, at least in children under 2 years of age. The organism is relatively insensitive to penicillin *in vitro*. A great advance came with the use of streptomycin but a substantial proportion of failures

occurred owing to streptomycin resistance developing, often within twenty-four hours. Nevertheless with the combination of streptomycin, intramuscularly and intrathecally, with sulphadiazine, Appelbaum and Nelson (1950) could report the low mortality of 3·4% in 90 cases, although 9 of the cases had severe residual neurological damage. In spite of the insensitivity of the organism to penicillin *in vitro*, the triple combination of penicillin i.m., streptomycin i.m. and i.t. and sulphadiazine yields excellent results. Nevertheless, the treatment of choice to-day is by chloramphenicol alone, because it is simpler, avoids intrathecal injections, and gives wellnigh perfect results in the minimum of time. This method provides an almost exact analogy with that of sulphonamides alone in meningococcal meningitis. The spinal fluid becomes sterile in at least two-thirds of the cases within twenty-four to forty-eight hours and in 100% within seventy-two hours (Prather and Smith, 1950; McCrumb *et al.*, 1951; and Schoenbach *et al.*, 1952). Clinical recovery is correspondingly rapid; there are virtually no relapses and residual neurological damage is rare. Complications have included a few cases of transient subdural effusion, which may absorb without treatment or may require tapping. My last 3 cases, all in children under 2 years, have been treated with chloramphenicol alone and have responded in this rapid way. After forty-eight hours, organisms could not be cultured from the spinal fluid, although in one case they were still seen in films; the cell count also dropped rapidly. The dosage in these children was 1 capsule (250 mg.) four-hourly for the first twenty-four hours, then six-hourly for seven to nine days. Bactericidal concentrations over 4 µg./ml. were maintained in the spinal fluid.

In this disease and in typhoid fever, chloramphenicol has had perhaps its greatest triumph. There is no sign yet of *H. influenzæ* type b developing insensitivity, but if it does, I would add sulphadiazine at once as an adjuvant, and, if necessary, streptomycin i.m. and i.t.

*Salmonella Meningitis* (S. typhimurium, &c.)

This also seems to respond promptly to chloramphenicol (Beene *et al.*, 1951).

*Other Bacterial Meningitides*

These are rare, and I have little experience of them. They are due to organisms of low pathogenicity some of which may be introduced at lumbar puncture. They include infections with *E. coli*, proteus, enterococcus (*Strep. fæcalis*), and *Ps. æruginosa* (*B. pyocyaneus*). They are all relatively resistant to treatment. Sensitivity tests are absolutely essential in order to determine the most suitable combination of drugs to use for the particular strain isolated. The absolute maximum dosage is required and even then it may be necessary to inject specially high concentrations into the cerebrospinal fluid. Thus chloramphenicol has been injected intrathecally and intracisternally without harm as a suspension of 62·5 mg. of the drug in 5 c.c. saline, and Aureomycin has also been injected in a special solvent, such as the alkaline glycine neutral solution prepared and used by Ainley-Walker and Bosanquet (1952).

In general, for such infections it seems well to start with streptomycin i.m. and i.t. combined with sulphadiazine, and change after twenty-four hours, or because of developing resistance, to chloramphenicol and sulphadiazine, or even to use all three drugs from the outset. *B. pyocyaneus* infections may require the rather toxic drug Polymyxin B. in doses of 5 mg./kg. daily i.m. in 4 divided doses and also one or two i.t. doses of 4 mg. (Alexander, 1952).

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**Dr. J. C. Broom,** Bacteriologist, Wellcome Research Institution, London:

*Leptospiral Meningitis*

The occurrence of a form of Weil's disease, without jaundice, and in which meningeal symptoms predominate, was recognised as early as 1916 by Costa and Troisier, who named it "spirochétose méningée pure". Although this variety is comparatively rare in infections with *Leptospira icterohæmorrhagiæ*, it is much commoner when some of the other serological types, such as *L. canicola*, *L. pomona*, and *L. mitis* Johnson are involved. Pigs are the carrier hosts of *L. mitis* and *L. pomona*, and the latter was found by Gsell (1944) to be the causal agent of "Swineherd's disease", an acute febrile illness which almost invariably presents signs of meningitis.

In Switzerland, where it has been intensively studied, swineherd's disease shows certain interesting epidemiological features, for it occurs almost exclusively during the summer months, among young men who tend pigs. Gsell and his colleagues found that youths were employed to clean out the pigsties and that, in hot weather, they customarily worked bare-footed. The organism is excreted in the pigs' urine, and the contaminated bedding acted both as a nidus of infection, and as a cause of skin abrasions to provide portals of entry. In winter-time, when boots were worn, the incidence was practically nil.

In typical cases of leptospiral meningitis the onset is sudden, and the temperature rises rapidly to 103° F. or higher. The patient complains of nausea, intense headache, and photophobia; prostration is marked, often to a greater degree than seems warranted by the general condition. Signs of involvement of the central nervous system may appear in the early stages, and include mental confusion, disorientation, vertigo, stiffness of the neck and a positive Kernig's sign, weakness, or even paresis of muscles. In other cases the initial fever is not accompanied by localizing symptoms, and it abates after a day or two but, following an apyrexial period, the temperature rises again and acute meningitis develops.

The clinical diagnosis of this form of leptospirosis is often very difficult, and there is no doubt that cases are occasionally missed. For example Broom (1951) detected 17 cases of Weil's disease and 8 of *L. canicola* fever when testing serum from 642 patients suffering from aseptic meningitis. The sera had all been sent to Dr. F. O. McCallum for viral tests, and leptospirosis as a possible cause had apparently never been considered.

The death-rate in these so-called benign leptospiroses is negligible, so the assessment of different methods of treatment is not easy. Symptomatically, the severe and intractable headache is an outstanding characteristic, and it is quite unaffected by drugs. Lumbar puncture, which may have to be repeated, does, however, generally give marked relief even if the tension of the cerebrospinal fluid is not abnormally high.

Drug therapy is disappointing, and there is no valid evidence that penicillin is of any value whatsoever. The effects of this antibiotic in the treatment of various forms of leptospirosis have often been acclaimed by physicians, but generally only a small series of cases has been observed. With large numbers the findings are quite different. For example Broom (1951) analysed 418 cases of Weil's disease which occurred in England and Wales from 1947–50 inclusive, and found that the death-rate for those treated with penicillin was 17%, whereas the rate was only 15% for the whole series. When patients who did not develop jaundice were excluded from the analysis, the case-mortality in cases treated with penicillin was 22%, as compared with 23% in a series observed from 1940–46, before penicillin was available for the civilian population.

Opinions differ about the value of some of the newer antibiotics. Brunner and Meyer (1949) found that streptomycin eradicated *L. canicola* from the kidneys of dogs, which had become healthy carriers as the result of treatment with penicillin; and dramatic effects with Aureomycin have been reported, but only in single cases (Lurie, 1949; Brainerd *et al.*, 1949; Batchelor and Todd, 1950). On the other hand Hall and his colleagues (1951) record that they obtained no therapeutic action in cases of leptospirosis treated with Aureomycin, chloramphenicol, penicillin, streptomycin, or Terramycin.

These workers treated 69 cases in all, but the numbers which received each of the antibiotics were small, and the infections were mostly mild in character, so their sweeping statement is not perhaps fully justified. It may therefore be worth mentioning a very extensive investigation which was made by Uhlenhuth and Schoenherr (1951), on hamsters infected with a highly virulent strain of *L. canicola* which invariably caused the death of untreated animals.

To provide an accurate basis for evaluating the effect of the drugs used, preliminary observations were made to determine the extent of the pathological changes which could be expected at the various intervals of time after infection when treatment was started. From the results obtained they concluded that chloramphenicol was completely ineffective. By contrast, Aureomycin and Terramycin had a definite curative action, even when administration was not begun until signs of infection were present.

It would, of course, be unwise to assume that exactly the same effects will be obtained in man but, until further evidence is available, Aureomycin and Terramycin appear to be the drugs of choice in the treatment of leptospirosis.

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**Mr. J. V. Crawford:**

*Surgical Treatment in Meningitis*

Surgical methods play only a subsidiary part in the treatment of meningitis. Destroy the bacteria and the inflammatory products and toxins can be looked after by the meninges without drainage of the C.S.F. or irrigation of its pathways. Nevertheless, operative procedures may be undertaken in connexion with meningitis for the following reasons:

(1) To prevent meningitis occurring.
(2) To assist in diagnosis of atypical cases of meningitis and in particular to detect some of its complications.
(3) To aid the introduction of antibiotics.
(4) To relieve or circumvent obstruction of the cerebrospinal pathways and the associated rise of intracranial pressure.

*The Prevention of Meningitis*

The importance of prompt and adequate treatment of open head wounds must first be mentioned. Scalp lacerations must be cleaned and sutured, preferably in two layers as emphasized by Cushing. In compound fractures of the skull, a thorough removal of all foreign matter, detached fragments of bone, and grossly damaged tissue must be made.

Fracture of the base of the skull involving the paranasal sinuses, with tearing of the overlying dura mater is a well-established cause of meningitis, usually pneumococcal. The infection may develop rapidly, or even after years, often preceded then by an upper respiratory infection. The diagnosis of such a dural tear is easy in cases with persistent cerebrospinal rhinorrhœa or with an intracranial aerocele; but in other patients not showing these complications, even with expert radiological help, the diagnosis may be difficult or impossible. The surgical treatment consists in exposing the tear and closing it, usually by means of a fascial graft. With the better control of suppurative meningitis by antibiotics, this operation is no longer the emergency procedure of some years ago. The patient can be maintained on prophylactic penicillin and chemotherapy, until he recovers from the causative injury, and the repair then performed as an elective procedure. In a rare case, however, the profuse escape of C.S.F. from the nose may make it impossible to maintain an adequate level of penicillin in the C.S.F. by the usual intrathecal dosage. If meningitis is already present in such a case it may be necessary to give penicillin by lumbar puncture two or three times daily, and to operate to close the leak immediately the acute stage of the infection has been overcome.

Fracture of the middle cranial fossa may establish a connexion between the middle ear and the subarachnoid space, thus giving rise to meningitis with or without escape of C.S.F. from the ear. In closed middle fossa fractures the communication between ear and brain practically always closes spontaneously, but after gunshot wounds dural repair may be necessary.

In the prevention of meningitis the earlier and more effective treatment of suppurative conditions of the ear and paranasal sinuses which is now practised has greatly reduced the frequency of meningitis as a complication of such conditions.

*The Diagnosis of Meningitis*

Though lumbar puncture and bacteriological examination of the C.S.F. establish the correct diagnosis in most cases there still remain a few which require other diagnostic procedures. If the meningitis begins with focal signs and evidence of raised intracranial pressure, it may be imperative to exclude a brain abscess. Lumbar punctures, in the presence of a space-occupying lesion within the brain, may well precipitate a herniation of the brain tissue with catastrophic results. Streptococcal meningitis is particularly dangerous in that a brain abscess frequently co-exists with the meningitis. Ventriculography or ventricular estimation is the established investigation when such a complication is suspected, and, in general, has proved safe and effective. Latterly, percutaneous carotid angiography has been used, particularly when it is evident that the intracranial pressure is high. This method does not affect the intracranial tension, and if the abscess lies in the cerebral hemisphere, it provides excellent localization. There is no doubt that ventriculography does occasionally exacerbate cerebral œdema

already present, with consequent deterioration in the patient's condition. However, it remains the surest aid to the diagnosis of an infratentorial abscess, if the clinical picture does not permit a firm diagnosis. The burr holes required for ventriculography also permit inspection of the subdural space, enabling an occasional diagnosis of those rare cases of subdural abscess or empyema, which may co-exist with suppurative meningitis; and finally the ventricular fluid obtained may sometimes give a positive culture when repeated examination of the spinal fluid has proved negative.

*The Introduction of Antibiotics*

Antibiotics injected into the lumbar subarachnoid space spread quickly, both into the ventricles and the cerebral subarachnoid space. When there is any suspicion of blocking of the lumbar sac (revealed usually by manometric tests and clinical deterioration in the patient's condition), frontal burr holes should be made and the antibiotics introduced into the anterior horns of the lateral ventricles. The cisternal route is, of course, also effective, but when there is severe head retraction or restlessness, it may be difficult or dangerous to perform cisternal puncture. Also there does seem to be greater liability to severe reactions to antibiotics from cisternal than from ventricular injection.

Purulent pacchymeningitis associated with leptomeningitis may require local instillation of antibiotics into the subdural space, usually through an indwelling catheter.

*Relief of Obstruction of the C.S.F. Pathways*

There are two varieties of obstruction to consider: First, *obstruction by purulent exudate*. This occurs in the active phase of the meningitis, and the treatment consists of drainage of the C.S.F. either intermittently or continuously, while the appropriate antibiotic therapy is continued. This complication is probably common, but practically always transient.

Second (and rarely), *obstruction by fibrous adhesions* coming on after the infection has subsided—sometimes after a prolonged symptom-free latent interval. Treatment of these cases often calls for open operation.

The diagnosis of an obstruction is suggested by clinical deterioration and positive evidence of intracranial hypertension. Frontal burr holes should be made, so that ventricular pressure and fluid contents can be estimated. In infants the lateral angles of the fontanelle permit direct needling.

If the obstruction is in the cisterna ambiens, a very common site, a "communicating" or "external" hydrocephalus is created and the pressure will be high both in the ventricle and the lumbar sac, for the obstruction is distal to both. In such cases it is evident that lumbar puncture is a very adequate way of draining excess C.S.F. and controlling the intracranial pressure.

If the obstruction is at the foramina of exit from the fourth ventricle or within the ventricular system, an "obstructive" or "internal" hydrocephalus is created, with high pressure and abundant fluid in the ventricles, low pressure and scanty fluid in the lumbar sac.

Confirmation of the obstruction in such cases may be obtained by observation of the rate of spread of either an innocuous dye or an appropriate antibiotic from the ventricle to the lumbar subarachnoid space.

Relief of intracranial pressure in these cases calls for ventricular tapping or drainage. In adults either method is applicable, but, in infants, drainage for any length of time is extremely likely to be followed by a C.S.F. fistula. Lumbar puncture is contra-indicated as likely to cause a herniation. Should the obstruction persist for more than a few days ventriculography or encephalography is called for to permit more accurate localization of the site of the obstruction and, in rare instances, operation may be necessary as soon as control of the infection is apparent.

Operations for relief of "internal" or "obstructive" hydrocephalus consist of either, (1) direct exposure and excision of the obstruction lesion, for example adhesions closing the foramen of Magendie or, (2) providing an alternative pathway for the C.S.F. This is exemplified by Torkildsen's operation, in which a catheter or polythene tube is passed into the posterior horn of the lateral ventricle and its other end is led into the cisterna magna. The tube is left in situ. The results are usually excellent.

Operations for relief of communicating hydrocephalus are considerably more limited. Obstruction at the cisterna ambiens cannot be removed surgically. Many highly ingenious operations have been devised to provide alternative pathways for the C.S.F., either by-passing the tentorial opening or permitting the C.S.F. to drain into another body cavity; none has proved consistently successful. As an example of the first method I might mention third ventriculostomy in which an opening is created in the anterior wall or floor of the third ventricle so that the C.S.F. can pass from the ventricular system straight over the convexities of the cerebral hemispheres. For a variety of reasons the relief afforded is usually temporary only. Examples of the second method are many, e.g. drainage by tube from the cerebral subarachnoid space into the lateral sinus or middle ear or from the lumbar sac into the ureter. At the best these operations should be regarded as temporary measures, pending re-establishment of natural pathways.

In conclusion, I will emphasize that these various operative procedures are required but rarely in cases of meningitis and even more rarely in the acute stages of the disease. Surgery remains subordinate to the main lines of treatment by antibiotics and chemotherapy. The importance of ascertaining the bacteriology of the infection at the earliest moment and its reaction to antibiotics cannot be overstressed.

# Section of Psychiatry

President—The Hon. W. S. MACLAY, O.B.E., M.D., F.R.C.P., D.T.M. & H., D.P.M.

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## DISCUSSION ON ABREACTION

**Dr. Gerald Garmany** (Physician, Department of Psychological Medicine, Westminster Hospital): Abreaction used to mean the process by which memories of suppressed or repressed experience were revived, and the associated emotions expressed in speech or action. This implied a traumatic theory of neurosis which was Freud's early assumption but which he repudiated later on. It is presumably in deference to this that the reliving of a traumatic episode is no longer always implied when we speak of abreaction, and the meaning has been extended to cover a purely biological discharge without content. My colleagues and I decided on this occasion to take the word in its wider meaning, leaving it to individual speakers to distinguish what they meant by the word if they felt such distinction to be necessary.

Abreaction is used both for diagnosis and for treatment.

*Diagnosis.*—Here I find myself largely in agreement with other workers. When drugs like ether, Trilene, sodium amytal, or Methedrine are used for the investigation of obscure psychiatric conditions, I doubt whether the term abreaction is appropriately applied. Abreaction sometimes occurs in the process of investigation but it should surely be regarded in these circumstances as an epiphenomenon. Nevertheless it would be readily agreed that these substances are occasionally of very great use in the elucidation of obscure stuporous states, or with patients who are very inhibited. In the case of the latter I am personally much more in favour of taking time and exhibiting patience, for when a short cut is adopted a considerable price is often paid in suspicion on the part of the patient.

*Treatment.*—If the literature of the last few years is examined it will be seen that treatment by abreaction has been applied to two quite different groups of cases. The first group includes patients exhibiting hysterical or dissociative phenomena while the second group includes those whose symptoms are compounded of tension in more or less overt form. It is perfectly true that many patients showing hysterical reactions show a certain amount of anxiety as well; and it is true that many patients with obvious tension may show hysterical colouring to their illnesses. Nevertheless, in any given case it is not usually difficult to say which one of these things predominates and the distinction may have important applications to treatment and prognosis. This difference was recognized a long time ago by William McDougall (1926), and also by Jung, both of whom stated that no relief could be expected from abreaction unless there was at the same time a recovery from a dissociated state; that is to say, relief of tension should not be the objective. Without denying the existence of mixed states let us consider these reactions separately.

*Acute hysterical reactions.*—There is no doubt that when dealing with acute cases under war conditions the use of abreactive techniques can relieve illness in a remarkable way; but the question arises as to how important these findings are from a practical point of view in the circumstances of peace. I think they are of very little importance except on purely theoretical grounds, for acute reactions of the kind we saw in 1940 and subsequently are very uncommon to-day. Most of the acute amnesias that one sees are on a very superficial level and respond quite readily to a simple approach without the use of any drugs at all. There are, of course, a certain number of hysterical conditions which are produced acutely and which respond to an abreactive approach, but these are so uncommon that they would not, by themselves, justify a claim that abreaction was a technique to be used frequently.

*Tension states.*—In the relief of tension I have not found abreaction to be of any use. In the last few years we have been reminded of some important theories which had been forgotten, and our attention has been drawn to apparent analogies in the behaviour of animals and human groups. These papers, written with great scholarship and great restraint, have shown an awareness of the dangers of drawing inferences too readily from such studies and applying them to individuals; but the same restraint has not always been evident in contributions from other sources. An objective assessment of the value of abreaction could well be hampered if the question were to be regarded as settled by apparently compelling evidence from the behaviour of animals and groups, and for this reason alone we ought to examine these analogies with some care. We should try to determine whether the inferences which have been drawn can, in fact, be supported.

It will be remembered that in the 1924 floods in Leningrad, some of the more nervous of Pavlov's dogs became highly excited when their lives were threatened and later passed into a state of stupor. On recovery it was found that conditioned reflexes which had recently been set up were now destroyed. Those dogs with a more robust nervous system showed greater immunity to the experience in that their excitement was less, there was less tendency to subsequent exhaustion, and the conditioned reflexes tended to survive. If a patient is put through a sufficiently harrowing experience in the form of an abreaction and he ends up in a state of exhaustion, then it may be thought that there are obvious similarities between this and the state shown by Pavlov's dogs. There is, however, very little in the behaviour or experience of neurotic patients which can justifiably be compared with the conditioned reflexes set up in such a difficult and specialized way in a dog. I have seen a state suggesting "ultra-paradoxical inhibition" in a sailor after returning from very heavy bombing at sea. I have seen such men almost stuporous in that they were practically incapable of spontaneous movement, quite disinterested and indeed quite unable to do very much for themselves. I never saw anything, however, which suggested a destruction of newly acquired patterns of behaviour except purely transitorily. Certainly there was nothing in the phenomenon which suggested that it might have any beneficial therapeutic effect. Nevertheless, if we use these Pavlovian concepts as modes of expression without imagining that they afford a rational basis for therapy, then they are useful and stimulating.

Comparison has also been made from various sources with the effects of alcohol. This is a comparison which is very difficult to follow, for most people who use alcohol do not particularly abreact in the process. While this drug is a very pleasant one I would prefer to regard it as a relaxant. It produces results which can be obtained quite effectively in other ways.

Finally and very importantly, certain phenomena known collectively as the conversion experience are stated to exist, and to afford evidence of the value of abreaction; and the number of papers in which this claim is made is now considerable. If the evidence as presented is acceptable it is of considerable importance, and should be examined with some care. I would dissent in saying that firstly, the facts are not as stated, and secondly, that the inferences to be drawn from the true facts, as I believe them to be, do not support abreaction in any way. In deciding what the conversion experience is we are largely dependent on the researches that have been made into the lives of people who are now dead. For obvious reasons those who have conversion experiences do not normally consult psychiatrists and since very few of us will have had such an experience ourselves our knowledge must be very limited. It is stated in one paper on abreaction that sudden conversion is often the first and essential step in bringing about a dramatic change in the patterns of thought (Sargant, 1948). I would submit that the literature indicates that it is nothing of the sort. Miss Evelyn Underhill (1911), among very many, says that even sudden conversion tends to follow a long period of restlessness, uncertainty, and mental stress; it tends to be the fulfilment of a long period during which personal synthesis has been attempted. Such arguments also ignore the fact that many conversion experiences are not sudden but very gradual and that for every St. Paul on the road to Damascus there is a George Fox. There is no evidence at all to suggest that sudden conversions have been more effective in transforming lives than have gradual ones and indeed the evidence is rather to the contrary. In Starbuck's follow-up quoted by William James (1947) the results of sudden conversion experiences tended to be rather dismal. I think it is wrong to refer to the conversion experiences which are quoted in "The Varieties of Religious Experience" by William James without also quoting William James's own comment upon them. This is, in fact, what he said: "there is no unmistakable class mark distinctive of true converts . . . the melting emotions and tumultuous affections connected with the crisis of change may all come by way of nature, or worse still be counterfeited by Satan". Caution should in any case be exercised in drawing inferences based on the experience of American revivalist meetings for, as James has pointed out, no other Protestant sect has set anything like the store by *instantaneous* conversion that the Methodists have. As Sargant has pointed out, Wesley took very great care after his disciples had been converted, to make sure that they attended at regular intervals in groups under a group leader. It is surely permissible to wonder whether such change as did occur was not due more to the re-education which followed than to the conversion experience itself.

Without being able to understand it one must concede the validity of the conversion experience since it has been reported over such a very long time from all quarters of the globe. I do not, however, accept that *emotional discharges* by groups of people bear the slightest resemblance to the conversion experience as traditionally described. The conversion experience as described in the literature is a *noetic* one while the experiences described in Wesley's journal are obviously of an *emotional* kind. We are therefore in the position that we have identified two entirely dissimilar phenomena and ascribed the effects of one to the other.

We have at Westminster Hospital been through the range of possible substances including an unusually extensive trial of carbon dioxide and the result was that we found it almost totally ineffective for any sort of condition in any sort of patient. Like Kindwall (1952) we found that a few patients became addicted to it.

I feel that abreaction is the wrong sort of approach, quite apart from the purely empirical fact that is it not of very great value in any sort of case other than the comparatively uncommon acute hysterical

reaction. Abreaction is not a very feasible proposition under the circumstances of ordinary life, and even when it is feasible it is almost invariably undesirable. It disturbs relationships with other people and it usually disturbs the individual himself. I cannot feel that repeated abreactions can possibly be a good therapeutic approach in the light of this fact, for we habituate the patient to something that, in fact, we would wish to stop. We are indeed heaping fuel on the fires which tend to consume him. Very often when our course of abreaction is over we leave him feeling slightly relaxed but more depressed and more guilty than he was before. I think we are in danger of stimulating his id when what he needs is support for a tottering super-ego. Kretschmer (1934) mentions two other ways of dealing with suppressed emotion apart from abreaction. He points out what is commonly forgotten, namely that spontaneous resolution can sometimes occur. More relevant to the patients with whom we deal is the other method of sublimation and the provision of psychomotor outlets. In his words as translated by E. B. Strauss, "Activity and work are the cornerstone and lodestar of psychotherapy".

I believe it is a perfectly practical proposition with a certain percentage of patients to teach the art of muscle relaxation purely as a muscular habit. Jacobson (1929) set out a technique for doing this about thirty years ago which has had very little attention in this country until very recently (Garmany, 1952). We have found at Westminster Hospital that this method can be taught effectively by a physiotherapist if she understands what the objective is and how the method should be applied. Combined with this training of a new muscle habit it is possible to teach some new mental habits as well. It is surely not straining credulity too much to suggest that one way of treating aggressiveness is to make some attempt to adjust the patient's sense of values so that aggression is aroused a little less frequently and a little less intensively. This is surely a much more sensible way of dealing with aggression than by providing periodic outlets for something which should not be allowed to accumulate.

We accept the limitations of constitution and of temperament far too easily. It is certainly true that a shop assistant can learn to cope with tiresome customers throughout a day and end that day tired but not torn asunder by suppressed aggression. It is equally true that a policeman, whatever his constitution, can be taught to conduct himself with that placid and sometimes infuriating calm which all of us know so well. Most doctors can learn to treat their patients with reasonable calm and detachment. The common factor in all these apparent changes of personality is surely to be found in the fact that the attainment of calm, which is what we are at the moment considering, is set up as an ideal of greater importance than anything else. The policeman and the shop assistant and the doctor would all probably say "As soon as I'm off duty this no longer applies and I can be myself". Nevertheless, what can be attained for one part of the day could equally be aimed at for the remainder if the incentive were sufficiently great, and providing a reasonable amount of energy and drive is available. In the case of emotionally disturbed people we can provide the incentive easily enough if we keep it simple and make sure it is one which will appeal to them. That incentive must, in fact, be peace of mind since it is the absence of this quality which has made them seek our help. If the patient can be persuaded that for a time at least he must subordinate all efforts to this one objective, results can very frequently be attained. If the patient is so dull that he cannot understand what is being suggested to him, then he is not likely to respond to any other kind of therapy. Equally, if he is a chronic neurotic with an absence of pertinacity and drive, then again the prognosis would usually be conceded to be poor with any sort of treatment.

My submission then is this. Abreaction has a large place in psychiatry in wartime when traumatic hysterical reactions are very common. In peacetime it is still a treatment of choice for acute dissociative states, though it is not usual to see many of these even in a general hospital where the incidence is probably higher than elsewhere. I merely echo what Sargant and Shorvon in particular have emphasized on many occasions, when I say that abreaction is not the treatment for tension states. I would submit that purposive teaching in relaxation augmented by a suitable type of psychotherapy is a natural and reasonable mode of approach to these problems; and that it gives rewarding results in a fair proportion of cases. When abreaction would but perpetuate anarchy, I would submit that it should be replaced by an effort to reconstruct the patient's habits and pattern of living; and even to instil some new attitudes and erect some new sentiments. For those of us blessed with health, abreaction can be regarded as a pleasant indulgence which can remain quite enjoyable providing it is not exercised too frequently. For the emotionally disturbed it can be nothing else but a tiresome disability. Damping down the fire beneath a bursting boiler is a good deal safer than taking its top off.

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**Dr. H. J. Shorvon:** Ever since work on the treatment of hysteria was begun in the last century, the value of the abreaction of old traumatic, emotional episodes has been recognized. It has also been stressed that a satisfactory clinical result is more likely where there is an intense emotional re-living of the experiences, rather than a dull recital of the facts. Freud confined the term abreaction to the emotional release that may occur when repressed material is brought into consciousness, but experience in the treatment of the acute war neuroses led one to incorporate conscious traumatic material in the concept of abreaction, and it is in this sense that I use it here.

Early in the last war, Sargant and Slater (1940) discovered that intravenous barbiturates facilitated this emotional release in acute psychiatric battle casualties. Thus, "drug abreaction" developed as an alternative to the older method of abreaction under hypnosis. Later in the war it became evident that the more long-standing the unresolved traumatic events, the more difficult the production of an effective abreaction under intravenous barbiturates. In 1944, following the method developed by Palmer, Sargant and I found we could often induce a more intense and satisfactory abreaction by encouraging our Normandy casualties to re-live their experiences under light etherization. We then made several observations relating to excitatory abreaction. Recently acquired neurotic patterns of behaviour following stress might be broken up by an intense abreaction, particularly if a climax of excitement is reached, and the abreaction pushed to the point of complete inhibition or dissociation or temporary emotional "collapse". Also, the intensity of the emotional excitation might be more important than the accuracy of the abreacted material. It is not necessarily essential to abreact specific incidents, or uncover all traumatic incidents, and a great release and relief of aggression or nervous tension may even follow a non-specific abreaction, thus paving the way to reintegration by psychotherapy. Moreover, one might on an occasion deliberately distort instances or even create artificial situations analogous to the traumatic experience, if it leads to a greater degree of emotional excitement. These findings are fully discussed in papers by Sargant and myself (1945), and Shorvon and Sargant (1947), which include details of the technique of ether abreaction. We also suggested that the mechanism of abreaction might be explained in terms of Pavlovian physiology and terminology. Briefly, it seemed to us that the persistent bombardment with traumatic stimuli in battle, with its production of primitive fear reactions and newly acquired neurotic patterns of behaviour by a process of conditioning in those constitutionally predisposed, bore a resemblance to Pavlov's experimental induction of neuroses in animals by the application of various conflicting stimuli in a confined experimental set-up. Similarly, as Pavlov found during the Leningrad floods that his drowning dogs, through intense excitement and fear, lost their elaborately built-up, recently acquired conditioned reflexes, so by intense excitatory abreactions, local areas of what appear to be induced cortical inhibition, such as patches of amnesia, paralysis, speech disturbances, &c., might be disrupted or broken up. A fuller discussion and extension of this theme is found in the papers already referred to.

It is generally agreed that the acute war neuroses are not essentially different from those seen in civilian life except in their greater severity, their tendency to occur also in better types of personality and their obstinate persistence or rapid extinction; the basic patterns of behaviour remain unaltered. We therefore extended abreactive techniques to the treatment of neurosis seen in ordinary practice. Certain difficulties and contra-indications soon emerged. The more chronic and ingrained the neurotic patterns attributable to traumatic events, the harder it has proved under ether to rouse the patient into a state of emotional excitement and the more difficult or impossible to obtain an end-point of exhaustion or dissociation. The patient with a reasonably stable personality who has broken down only under severe stress, and shows hysterical and anxiety symptoms, was the most likely to respond to, and benefit from, attempts at abreaction under ether. The gross hysteric, however, is usually unsuitable in that there is a much too rapid dissociation as soon as a minimal significant stimulus is applied, and abreaction is thus prevented or interrupted. Depersonalization in a hysterical setting, aggressive psychopathy, and some psychosomatic disorders apparently precipitated by psychological trauma, may also be helped. On the other hand, endogenous depressives, as expected, generally give a dull recital of events, and obsessional patients are too rigid and exact to re-live with emotion an incident not actually happening at that particular moment; they are unable to lose themselves. An attempted abreaction may well render the obsessional patient temporarily more tense. Only where there is a marked hysterical component to the obsessional illness is a useful abreaction possible.

In 1948 Meduna published his first account of what he called a "pharmaco-dynamic treatment of psychoneuroses" using repeated inhalations of a mixture of 30% carbon dioxide and 70% oxygen. He claimed that some psychoneurotic patterns of behaviour could be broken up by repeated cortical stimulation with this inhalation mixture, without any concurrent systematic psychotherapy. A modified technique with the specific aim of producing abreaction was described by Milligan (1951). In 1947 Dr. Sargant, using Meduna's technique, abreacted and successfully resolved an amnesia in two patients who had been unsuccessfully treated by other methods. Since then a large-scale investigation has been undertaken on the practical applications to the neuroses of this treatment, at St. Thomas', Belmont and the National Hospitals. The patient is encouraged to abreact either as he is about to lose consciousness or when coming round again, and the abreaction may be prolonged by suitably regulating the flow of the gas. Ether, Methedrine or nitrous oxide may be used in

combination with the carbon dioxide to produce the desired effect, and we have observed in some cases that the immediate use of carbon dioxide after a moderate ether abreaction enables the patient to obtain that climax of excitement which leads to effective emotional release. The rapid substitution of nitrous oxide, or rapid alternations of nitrous oxide and carbon dioxide, may also be used to obtain a desired quality of abreaction. Again, this treatment appears to be of value in patients of good basic personality with hysterical features incorporated in their neurosis, the results of traumatic episodes. That is to say, it is useful in uncovering an amnesia or abolishing a conversion symptom such as a paralysis or tic, and in "traumatic" anxiety states characterized by restlessness, irritability, sweating, palpitations, insomnia, bad dreams and difficulty in settling in a job. I cannot emphasize too strongly that obsessional and tension states may be made much worse. Sargant and I have frequently stressed the difficulties, and possible dangers, in attempting to abreact patients suffering from obsessional neuroses. The practical advantages of the treatment in selected cases are its convenience, safety, economy of time and ease of administration. In the "psychosomatic disorders" such as neurodermatitis, we have occasionally obtained some relief of tension, but on the whole the results have not been favourable, probably because the tension is usually in an obsessional setting. I believe many failures with carbon dioxide therapy are due to its use without active attempts being made to abreact the patient. A spontaneous abreaction of a phantasy may occur during a carbon dioxide abreaction. For example, a solicitor patient, aged 34, complained of depression, insomnia and losses of memory since serving as a major in Italy in 1945, whereas he had previously been an energetic, cheerful, easy-going person and a good mixer. From 1948 he began to suffer from fugues, and eventually shock therapy was tried in another hospital, with little or no benefit. After admission to Belmont he described various traumatic incidents whilst serving in the Army, culminating in an amnesia in Trieste. Under ether abreaction he showed much affect over his responsibility for the death of a partisan's daughter, aged 12, whom the patient, as a secret agent, had sent on an unnecessary errand. He improved considerably after four ether abreactions and fifteen carbon dioxide treatments, but it was only when he was vigorously abreacted under carbon dioxide that he suddenly became wildly excited and believed he was being questioned by the Gestapo in a concentration camp. He had never been in one, but for many years ruminated and phantasied over what would take place there if he were caught. He became symptom-free after this intense abreaction.

During the past six years I have made extensive use of intravenous Methedrine as an abreactive and psychotherapeutic aid, following the work of Simon and Taube (1946) and Sargant (1948). Usually, an emotional disturbance follows almost immediately on the first intravenous injection of 15–30 mg. of Methedrine, and this effect has aptly been called "Methedrine shock" by Professor Jean Delay. I generally prefer to administer 20 mg. in the first treatment. The patient often exhibits bouts of weeping, restlessness and anger. Some complain temporarily of dizziness, pains in the back of the head, rapid respirations, a surging feeling in the chest and epigastrium, palpitations, tingling, numbness and coldness of limbs, mild sweating, dryness of mouth and other autonomic effects. A prolonged stage of marked relaxation soon sets in. The patient who was previously tense becomes calm, relaxed, self-confident and talkative. There is a clarity of mind, clear memory of details, acceleration of ideas and an alertness and euphoria which together occasionally present an almost hypomanic appearance. The emotional facilitation soon ceases to be intense, but continues in a milder form for some hours. In other words, the drug produces a prolonged moderate excitation in full consciousness. It is helpful in establishing confidence and rapport and allows the reticent patient, who might otherwise give up treatment, to carry on. Inhibition and reserve are often swept aside, so that much significant material may pour out in a short time, and can be synthesized in clear consciousness. The material is frequently of a nature that the patient had no intention of disclosing so quickly, and differs from what appeared to be important at ordinary interview. The pressure of talk may continue in this fashion for several hours, and if the patient is left to his own devices he tends to write voluminously. I encourage patients to write after interview and much valuable material is assembled, since the writing is uninhibited and the patient is able to concentrate. A schizoid patient with depersonalization said he believed the three main effects of Methedrine were "to rev up mental processes, remove the woolliness from the mind, and produce relaxation". Another schizoid depersonalized patient said that after Methedrine "there was a complete slashing of the social façade. With the first injection I could not talk or write fast enough. My mind went round so fast that I did not get out half. Later I was more calm and wanted to talk, but not in particular". An obsessional doctor patient said that "verbal conclusions, previously reached during analysis, were felt as absolute truths under Methedrine, their expression in words coinciding with euphoria and a dramatic loss of tension". Explosive outbursts may occur, such as during the breaking up of an amnesia. The abreaction may be intensified if, at the more critical points, an ether mask is applied. The patient may then become wildly excited, shout, fight or cry. In practice I often combined ether with Methedrine at some stage of the treatment. A combination of intravenous Methedrine and barbiturate may also give an enhanced abreaction, but the patient may present a noisy drunken state instead. It has been our practice to prescribe 6 grains of sodium amytal by mouth several hours after a Methedrine abreaction with a view to ensuring some sleep, but it often has the reverse effect and seems to endow the disinhibiting effect of the Methedrine with renewed vigour. Adverse effects include loss of appetite, sleeplessness on the night of the injection,

and the emotional lability that may ensue for many hours after the injection may render it inadvisable for the patient to be left entirely on his own. Tension of the jaw muscles with clenching of teeth is common, and the patient may experience a prolonged exacerbation of tension several hours after the injection, so much so that heavy sedation may be necessary. A reaction often sets in next day with complaints of depression and tiredness. It is possible that some of the depression is due to guilt over bringing up unconscious material. Very occasionally one encounters a marked hysterical reaction lasting some days, and the patient complains of vomiting, exhaustion, collapsed feelings, limpness and weakness of limbs. Repeated slow intravenous injections of acetylcholine may damp down and counteract excessive excitement and tension following the injection.

The manifestations of "Methedrine shock" are much less obvious with each consecutive injection, and it is a curious fact that the abreactive intensity of the first injection is rarely repeated. I find no practical advantage in increasing the dose beyond 30 mg. and if this is much exceeded an inhibitory response may ensue. It is interesting that hysterical patients often feel sleepy and tired immediately after a Methedrine injection, becoming inhibited instead of stimulated, and this may be striking and diagnostic. It is advisable to limit the dosage in such patients to 15–20 mg.

The choice of drug for abreactive purposes therefore largely depends on the history and previous personality of the patient. Intravenous barbiturates, ether and carbon dioxide are useful in recent acute traumatic neuroses, and ether or carbon dioxide may be used in more chronic cases of this kind with anxiety and conversion symptoms. Methedrine can equally be used in those cases, but it may also be of value where there is some admixture of obsessional symptoms in the total picture which hampers the effectiveness of the other drugs. This peculiarity of Methedrine in helping that patient so difficult to treat, namely, the neurotic with an obsessional personality or with obsessional traits, obliges one to handle it with great care. It breaks down resistance and allows the obsessional to disclose material he is hardly likely to do otherwise. Particular care, however, must be taken with obsessional patients who are paranoid, as these traits become more prominent as a result of injudicious treatment. The drug should be discontinued, or restricted to a small dose. Also, since it induces introspection, there is a real danger of its flaring up symptoms in the obsessional.

Phobic anxiety states with panic attacks usually necessitate long-term psychotherapy, and physical methods, apart from sedation, modified insulin and intravenous acetylcholine injections, are limited in their application. Such patients tend to have obsessional components which prevent them from responding to abreactive techniques under ether, $CO_2$ or barbiturates. Intravenous Methedrine, however, by its facilitation of emotional release and prolonged action allows a slow relief of tension, and by its acceleration of ideas and revival of latent or buried material in clear consciousness, allows the patient to gain rapid insight and connect up events leading to his illness. This is especially so where there is also a hysterical element in the total picture. Methedrine can thus play a useful part in the treatment of tension states where the obsessional component is not too marked, by a gradual reduction of tension with repeated injections. Some phobic patients have a fear of ether, but under Methedrine they develop a care-free attitude so that ether, if indicated, can then be used to enhance the excitatory effect of Methedrine.

Dr. W. A. H. Stevenson and I have developed a method of inducing hypnosis in resistant subjects, especially obsessionals, by exciting them or distracting attention, rather than by focusing it or using sedation. We found in an obsessional male of 30 suffering from depersonalization, whom we were treating abreactively with Methedrine and ether, that a considerably greater degree of abreaction could be obtained once he was hypnotized. Our method had been to use ether and Methedrine and then induce hypnosis in the conscious but excited stage. Later we found that by catching the patient out with a sudden question during the hypnotic patter or by asking him to count, or recite while one is making sleep suggestions, hypnosis could be easily induced.

States of depersonalization were included in our early attempts at abreactive therapy. We had only occasional successes with abreaction under ether but the majority of patients were rigid obsessionals and failed to abreact by this method. Methedrine, however, has sometimes proved beneficial in breaking up the inhibitory state by its powerful cortical stimulation; unreality and lethargy can thus sometimes be abolished by repeated injections.

In a previous communication (1950) I discussed the use of Methedrine and other methods of "drug abreaction" in the treatment of chronic skin disorders, such as neurodermatitis and pruritus, in which psychological factors appeared to play an important part.

I have therefore found intravenous Methedrine abreactive therapy of value in some phobic states, some states of depersonalization, "traumatic anxiety states", psychosomatic disorders and mixed obsessive tension states with a marked hysterical overlay. In all these cases hysterical components are of good prognostic significance, whereas the patient's condition may be aggravated if the obsessional component is marked or the tension and anxiety are acute.

In conclusion, two main points emerge:

First, abreaction must be regarded, not as a complete and isolated thing, but as part of an all-round approach to treatment by psychotherapy and physical methods. For example, it is often necessary

to remove some outstanding conversion symptom and improve the physical state of the patient before psychotherapy is attempted. If the patient's mind is relieved of the tension associated with certain "complexes" or past traumatic events, it is obviously also necessary to help readjust his personal relationships and problems. This can be done by systematic psychotherapy.

Second, abreaction is in no sense a panacea. It is merely a type of treatment of particular value for certain types of neurosis, cases in which abnormal inhibition and dissociation are prominent factors, such as traumatic hysterical states and tension states with hysterical features. It is thus a short-cut treatment for the very group of cases which benefit from analytical treatment. In other types of psychiatric disorders abreaction has not proved of value, and may even be positively harmful.

With regard to Dr. Garmany's criticism of our relating these procedures to sudden religious conversions, I remain convinced that abreactive phases occurring in different cultural settings are often related phenomena though given different explanations according to the cultures in which they occur. Nor do I think that Dr. Garmany has provided evidence to the contrary in what he has said. We have dealt with this evidence fully in a series of papers ("Excitatory Abreaction", Shorvon and Sargant, 1947) and in this contribution I have confined myself to the practical aspects of our work, which is of greater utility than theory.

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**Dr. S. Lowy:** Eleven cases of severe psychoneuroses receiving intense analytical psychotherapy were also given occasional ether stimulation. This measure proved effective through the vividness of memories, emergence of repressed elements confirming the therapist's conjecture, and the bringing to light of particulars not yet detected during weeks of analytical work.

In contrast to the barbiturates, ether acts partly through stimulation and not through de-inhibition alone. Some of the patients were subjected to Pentothal as well as to ether, but the response to the latter was incomparably more useful.

As a rule, ether excitation in the treatment of classical neuroses should be tried only after a period of analytical work. In one case, however, it was applied from the outset and made the patient fit for analytical co-operation, even though for the preceding ten years this approach had been resisted by him.

Ether excitation can be used without abreacting a certain trauma or a definite affective complex, merely for inducing the patient to scream and roll about. Thus, general inhibitions are broken down, and this may pave the way to memories and phantasies becoming conscious, possibly hours after the drug effect has ceased.

Ether stimulation has also proved useful for amplifying desirable tendencies. Thus it has been possible to aid the development of inhibited libido, and, in particular, of hetero-sexual tendencies in male homosexuals receiving analytical treatment. Even though the patient may have already attained the capacity to feel libido towards a female partner imagined under ether excitation, he may not be able to feel anything in connexion with infantile memories of a sexual nature if the original impression had not been experienced with libido. On the other hand, sexually frigid women and homosexuals having analysis because of other kinds of complaint may, under ether, experience orgasm and heterosexual desire respectively, even though outside this artificial situation they remain unchanged in this respect.

For example, a woman suffering for years from a paranoid idea, a few compulsions, and insomnia, had been told that the latter complaint had been due to her husband's impotence. At the same time she had been pronounced unsuited for analytical treatment and essentially a neurotic by constitution. After her husband's cure, however, she felt no change; and, peculiarly, her resentment against him grew stronger. She asked for psychological treatment, and improved very much. During its course it became clear that she was, and had always been, genitally frigid. At an advanced phase of her treatment a few ether abreactions were applied, and much corroborative material was elicited, and the total amnesia for a severe trauma was lifted. As a side-effect, on two occasions the patient felt "a kind of orgasm", for the first time in her life. Subsequently, she had her psychological treatment reduced to once a week or fortnight; and there was not only further general improvement, but also some unmistakable genital responsiveness developed.

If ether excitation does not aid the analytical treatment, it becomes merely a dynamic equivalent of a trauma or the anomalous sexual pattern. In cases with therapeutic gain the force of this phenomenon decreases with the progress achieved.

Occasionally the material elicited through ether undergoes secondary repression; but it is always easy to cope with this complication.

If presented with a certain theme for abreaction, the patient may at first accept it, but with the growing excitation he may suddenly go over to another mental element, as a rule much more traumatic. This illustrates to patient and psychiatrist alike the reality of associative processes and the dynamic link of various affective elements.

At various stages of the analysis the subject's response to ether may vary; on subsequent occasions it may be greater, or smaller than before. I tried to approach chronic inhibited patients with ether after a few analytic interviews; their response was poor in comparison with the eleven neurotics who were of very similar types but had received sufficient preliminary treatment. However, the aid afforded by ether in our cases was not always dependent on strong abreaction, and not proportionate to its degree.

A number of patients were unable to respond intensely. 5 out of 7 such subjects were conspicuous in that they did not consciously feel negative transference during their treatment, even though ether was given to them after their inhibitions had been substantially alleviated. Their parents or other relatives were psychopaths, and the patients seemed to have inherited a vulnerable disposition, easily harmed by unfavourable early influences. However, in ordinary life they were fully capable of hatred and aggressiveness; they were only unable to develop transference hostility towards a person who gave them but help and sympathy.

Though as a rule rigid or obsessive personalities are unable to abreact, one ruminative and two compulsive patients responded intensely to ether.

Within the analytical treatment of compulsive neurotics ether excitation has proved of some value in all cases, and a substantial aid in three instances.

If repeated abreactions reinforce the undesirable pattern, a sedative course of insulin should follow immediately. It may be an omission not to abreact pressing material even though increased anxiety may result. Admittedly, the ruminative, tense patient, who is likely to react unfavourably, is as a rule unsuited for analytical therapy. Paranoic personalities were always excluded, and in the others abreaction was never perceived even unconsciously as aggression. Within a well-conducted analytical situation it is easy to remedy unpleasant reactions to ether excitation that would be deemed harmful otherwise.

The sudden emergence of traumas after years of severe compulsive illness may lead to the patient's dwelling on these memories and becoming depressive or suicidal. It has always been possible to cope with this outcome and make the new misery much less painful than the original illness.

Drug excitation in all these neuroses can only aid the analytical process provided this treatment is indicated. It has no influence on the basic dynamism of neurotic obsession and compulsion, ideas or reference, sexual inhibitions, or even anxiety or insomnia associated with some of these symptoms. Drug excitation does, however, affect *basically* those conditions where abreaction in the narrower sense has proved the main remedy. Thus the difference between various types of neuroses is not only thrown into relief by their characteristic forms, but may also be indicated by the relationship of their basic processes to the experience of abreactive excitation.

In the type of cases here referred to, ordinary abreaction without analysis is of no use. It is necessary for the psychotherapist to be acquainted with the pertinent analytic particulars, and conduct the ether sessions accordingly. The patient, on the other hand, must have gone through the analytical process, for a varying period, if the fullest benefit is to be achieved from the excitatory sessions. It is true that two patients were subjected to ordinary abreaction in the midst of their systematic psychotherapy; this was performed by another psychiatrist. As a result, their subsequent co-operation in the continued analysis improved.

A favourable response to ether excitation itself is no guarantee of the success of the continued analytical treatment. Too much should not be expected from this difficult combined technique. Hard work on analytic and re-educational lines remains the non-surgical means of coping with severe neuroses. We may wish for the discovery of much improved physical methods to enable us to dispense, in most cases, with the time-consuming analytical treatments. At present we can only shorten to some extent the long periods now considered necessary for psychotherapy; and it is certain that the judicious use of ether is an efficient aid.

In response to questions and critical comments Dr. Lowy said that the type of analytical treatment he had in mind was outlined in his Introduction to the 1950 revised edition of W. Stekel's "Technique of Analytical Psychotherapy" (London). Within this framework, ether excitation and similar physical measures are not foreign technical elements, as they admittedly must be in ordinary psychoanalysis.

# Section of Dermatology

President—G. B. DOWLING, M.D., F.R.C.P.

[*December* 18, 1952]

**Six Cases of Lupus Vulgaris Treated with Isoniazid.**—G. B. DOWLING, M.D., F.R.C.P., E. WADDINGTON, M.D., M.R.C.P., R. G. HOWELL, M.R.C.P., and D. L. REES, M.R.C.P.

*Case I.*—Mrs. O. B., aged 51.

*History.*—The lupus began on the left cheek at 1–2 years, gradually spreading.

She had numerous treatments, including:

1935: Radium plaque.
1938: Finsen light.
1944/46: Treated with calciferol at St. Thomas's Hospital.
1946: Skin grafting carried out successfully.

*Treatment.*—Since then the lesions remained inactive until June 1952, when she was found to have an active lupus nodule in the lobe of the left ear. She was given isoniazid:

200 mg. daily for two months.
300 mg. daily for one month.
200 mg. daily for two months.

On 300 mg. daily she felt unwell and the dose was reduced to 200 mg. After two months the nodule was softer and after three months it had flattened considerably. It had disappeared after four months' treatment.

*Case II.*—Mr. C. L., aged 44.

*History.*—In 1942 he attended St. Thomas's Hospital with a twenty-year history of lupus vulgaris affecting the right side of the nose and upper lip. There was no mucosal involvement. In 1942 Eulykol injections produced considerable improvement.

In 1944 calciferol therapy was begun but the patient only attended for two months.

He was not seen again until August 1952 when he presented with numerous infiltrated nodules on the tip of the nose extending on to the upper lip and right naris.

*Treatment.*—August 1952. Isoniazid 400 mg. daily commenced. After four months' treatment the nodules have disappeared and there is minimal scarring. There were no toxic effects.

*Case III.*—Mr. E. S., aged 40.

*History.*—Single area of lupus vulgaris. This started at the age of 7 at the outer angle of the left orbit.

The origin of the adjacent sinus is thought to have been an inflammation, possibly tuberculous in origin, of the underlying bone. A radiograph revealed no underlying bone changes.

1941: Radium plaque applied.

June 1951 to April 1952: Calciferol therapy with partial regression, and some flattening only.

*Treatment.*—He was then put on a course of isoniazid when some improvement was noted within a month. This was progressive, and resulted finally in complete flattening of the plaque of lupus to give the present appearance with little if any clinical evidence of activity.

*Dosage.*—At first 250 mg. once a day of isoniazid, then increasing to 250 mg. twice a day. There were no toxic effects.

*Duration of treatment.*—Seven months.

*Case IV.*—I. C., female, aged 44.

*History.*—Thirty years' history of lupus vulgaris affecting "chin-strap" area of neck.

Calciferol therapy commenced in 1946 and continued with rest periods until March 1948. At this time there were no signs of clinical activity.

In August 1952 she presented again with numerous nodules in the scar.

*Treatment.*—Isoniazid—dosage: 200 mg. daily for two weeks and then 300 mg. daily for two months. There was marked improvement after six weeks. All the nodules had flattened and scaling had occurred. After four months' treatment there are one or two pigmented macules in the scar. No toxic effects.

*Case V.*—L. H., female, aged 63.

*History.*—Duration of lupus vulgaris on the left cheek: forty-seven years. She was first seen in 1944 when she had an irregular scarred area on the left cheek with nodules at the edge and in the centre of the scar.

*Treatment.*—June 1944 to July 1950: Calciferol therapy with rest periods. She never developed signs of toxicity nor was there much improvement.

July 1950: Streptomycin and PAS. After a six weeks' course there was slight flattening of the nodules.

August 1951 to May 1952: Thiosemicarbazone 200 mg. daily. After two months' treatment there was some improvement but despite continued treatment new nodules appeared in the centre of the scar.

June 1952: Isoniazid commenced with a dosage of 200 mg. daily for the first two months, and then 300 mg. daily for a further two months.

*Progress.*—After one month all the nodules had flattened and their surface became scaly. Improvement was maintained and after fifteen weeks' treatment she developed erythema nodosum on both lower legs and simultaneously the left cheek became swollen and red. Treatment was stopped and this reaction subsided in three weeks. The lupus vulgaris appeared to be clinically inactive and only pigmented macules were present in the scarred area. She has had no treatment for the past two months. There have been no signs of toxicity.

*Case VI.*—Mrs. M. M., aged 67.

*History.*—Large sheet of lupus starting in childhood, and involving the right side of the face.

Intermittent treatment with calciferol since 1946. This had to be discontinued on several occasions because of nausea and vomiting and urinary symptoms. The lupus improved but many active nodules persisted in the scar.

*Treatment.*—Course of isoniazid: At the beginning of treatment, a crop of raised lupus nodules was scattered throughout the scar tissue. Response was rapid and at the end of four months' treatment no infiltrated nodules remained and only a few pigmented macules were present. No toxic effects. Dosage: 300 mg. daily.

*Comment.*—We have presented 6 out of 15 cases of lupus vulgaris which have been treated for at least four months with isoniazid. Of these 15 cases all except one had previously received calciferol for a prolonged period and had either relapsed or had proved resistant to the treatment. Some had also been treated in addition with streptomycin and with thiosemicarbazone. The dosage of isoniazid was initially 3 mg. per kg. body-weight per day but after two months this was increased to 6 mg.

*Results.*—All the cases, with the exception of one patient on whom treatment was abandoned because of toxic effects, showed striking improvement within one month. Nodules arising in scarred areas rapidly flattened. After four months' treatment only 2 cases showed any clinical evidence of activity.

*Toxicity.*—Toxic effects occurred in 4 patients. One patient developed severe vertigo and a coarse tremor of the hands within a week. After a rest of two weeks a dose of 50 mg. per day was tried but the symptoms returned and treatment was abandoned.

The second patient developed extreme fatigue and numbness of the head after two months' treatment with a dose of 3 mg. per kg. Her lupus was at that time clinically inactive and treatment was stopped. She has been followed for a period of three months and no relapse has occurred.

The third patient developed fatigue and an enormous appetite and put on a stone in weight after being treated for seven weeks. The lupus had improved but there were still signs of activity.

The fourth (Case V) developed erythema nodosum on the legs and swelling and congestion of the lupus area after fifteen weeks' treatment. This reaction subsided within three weeks and the lupomata had flattened, leaving pigmented macules in the scar.

**Lupus Vulgaris Treated with Isoniazid.**—G. B. Dowling, M.D., F.R.C.P., and R. H. Seville, M.D., M.R.C.P.

A. F., male, aged 37.

*History.*—For the past twenty-one years the patient has had a slowly growing area of lupus vulgaris of the skin over his epiglottis. Ten months ago he noticed a lump in his hard palate, and biopsy at the Institute of Dental Surgery showed this to be lupus. Mr. D. Downton therefore referred him to St. Johns' Hospital for treatment.

1912: Small area of lupus on the lower part of left leg, clearing with "blue ointment" in one and a half years at age of 7. 1929: Area of lupus vulgaris under chin "following blow on tuberculous gland of neck" one year previously. Lesion cleared; cauterized and general ultraviolet light given for six months. 1931: Patient noticed onset of lesion over epiglottis (*vide supra*). 1937: Abscess left buttock and outer right thigh, leading to the diagnosis of tuberculous spine.

*On examination.*—A typical lesion of lupus can be seen over the epiglottis measuring 3·8 × 3·8 cm. Under the chin there is a scarred area of older lupus which contains active nodules. On the right side of the hard palate a pale brown infiltrated area is present measuring 0·3 × 0·6 cm.

*Special investigations.*—X-ray chest: shows adhesions at the right lung base and a healed calcified shadow in the left middle zone. There is no evidence of any active lung disease.

Mantoux: 1 : 10,000 negative. 1 : 1,000 positive.

*Treatment.*—Treatment with isoniazid (100 mg. t.d.s.) was started six months ago. All the active lesions looked paler and flatter at the third week. After six weeks' therapy there were no signs of the palatal lesion and only a few ghost lesions could be seen on the neck. These latter have disappeared following a three months' course of calciferol (100,000 i.u. daily) and a further six weeks' isoniazid (150 mg. three times daily).

*Comment.*—Calciferol was given as an alternative therapy as it was thought that the tendency for developing drug resistance would be reduced by limiting the length of the courses.

**The President:** We have shown these cases, not because we suppose that we have had more experience of the treatment of lupus with isoniazid than many others, but with the intention of comparing notes. The drug Nydrazid (isoniazid) was made freely available to us at St. Thomas's Hospital at the earliest possible moment through the kindness of Dr. Geoffrey Rake.

In addition to the 15 cases so far treated at St. Thomas's, 4 in-patients have been treated at the Morland Clinics at Alton, 2 previously untreated and 2 old cases which had been treated both locally and with calciferol. All 4 were clinically cured within less than four months, that is, none of the characteristic lupomatous nodules can now be seen. One case of severe senile tuberculous adenitis with multiple discharging sinuses, treated in the out-patient department at St. Thomas's Hospital, has cleared up completely in about the same period.

The speed and reliability of this treatment have greatly exceeded that of calciferol and of calciferol combined with streptomycin, while with thiosemicarbazone we never achieved any striking degree of success. We are now abandoning treatment for new cases with isoniazid alone in favour of the treatment advocated by Joiner and others (1952, *Lancet*, ii, 843), that is the combination of isoniazid and streptomycin.

**Dr. Brian Russell and Dr. N. A. Thorne:**

*Progress Report on 15 Cases*

**Dr. Brian Russell:** We wish to make a progress report on 15 patients who have been treated with isoniazid for periods varying between nine and thirty weeks. We have adopted strict criteria of improvement—it is only permissible to contemplate the possibility of "cure" of lupus after all physical signs of activity have been absent for at least five years. After clinical cures from all forms of treatment used up to the present, biopsies have sometimes revealed the presence of tubercles in apparently healed areas. Time alone can tell whether isoniazid will prove the exception by removing histological as well as clinical evidence of tuberculosis.

In our trial, then, clinical clearance is taken to mean the disappearance of all redness, infiltration, scaling and "apple-jelly" nodulation. If the faintest scaling or brownish discoloration remains at the site of a nodule, progress has been described as marked (3+). If there is slight residual infiltration, with scaling and increased opacity of the lesions the grading has been moderate improvement (2+). Slight improvement (1+) infers a diminution of redness, infiltration, scaling and translucency. All observations of progress have been controlled by photographs, using the same factors of lighting, exposure, &c., throughout.

The minimal reasonably effective dose for an adult seems to be 100 mg. three times a day and we have given 100 mg. four times a day to some patients who have not responded well enough to the smaller dosage. We have given the drug orally or by local intralesional injections or by a combination of these methods. With oral treatment, a steady and quiet improvement takes place, without early exacerbations such as are often observed with calciferol. The effect of isoniazid seems to be on the organisms and that of calciferol on the host and there seems no reason why the two treatments should not be given together if desired.

**Dr. N. A. Thorne:** I will describe a few illustrative cases:

*Case A.*—A woman, aged 47, had suffered from lupus vulgaris for eight years. She had been treated previously with carbon arc baths and the Finsen-Lomholt lamp: the latter had caused severe reactions with only slight improvement. After twenty-seven injections of 50–100 mg. of isoniazid weekly there was moderate improvement (2+).

*Case B.*—Woman, aged 52. I showed her to this Section in April 1952 on behalf of Dr. W. J. O'Donovan. Her extensive lupus of the face and neck had remained untreated for over thirty years. She was given isoniazid by mouth 300 mg. daily and daily carbon arc baths to the trunk and the face and limbs only, the neck being shielded from the light rays. Before treatment there were closely packed raised nodules surrounded by a purplish-red discoloration, erythema and considerable scaliness (Fig. 1). After thirty weeks much of the erythema had been replaced by pigmentation and although active nodules with scaliness still persisted on the pinnæ and over the angles of the jaw, there was almost complete flattening of nodules and absence of scaliness over the greater part of the face, and discrete nodules over the shoulders had been replaced by pigmented scars (Figs. 2, 3 and 4). Improvement marked (3+).

*Case C.*—Man, aged 48, with surgical ankylosis of one knee-joint following tuberculosis. He had suffered from lupus for thirty-four years, the right side of nose, "chin-strap" area, occiput and palate being affected. Light treatment had been used with success in the past but relapse had recently occurred. Isoniazid 300 mg. daily was given for eighteen weeks and at this time all lesions were regressing, nodules becoming flatter and scaliness disappearing. Improvement moderate (2+).

*Case D.*—Woman, aged 51, with lupus of ten years' duration which had been treated with ultra-violet rays and with calciferol. She developed pulmonary tuberculosis which had become quiescent following rest, streptomycin and PAS. The lupus responded poorly to all these remedies and it was decided to give isoniazid by local injection lest its oral use might produce drug-fast organisms and so detract from its possible future value in the control of the chest condition. Nineteen weekly local injections of from 50–250 mg. of isoniazid were given into the active lupus over the right elbow, without any definite improvement. This was our only complete failure by either method of administration of isoniazid (No change).

*Case E.*—Man, aged 31. He had had a nephrectomy performed four years ago for unilateral renal tuberculosis. Lupus first occurred twenty-seven years ago. Ultraviolet rays had cleared one lesion behind the left knee but active nodules remained amidst scar tissue above the right patella. Following twenty-six weekly injections of isoniazid locally the nodules had become much flatter, scaliness had disappeared and all local pain and discomfort had ceased. His was the only case under review to develop any complication—a mild degree of urticaria which did not interfere with continuation of the injections. Improvement moderate (2+).

*Case F.*—Man, aged 36. He had suffered from lupus over the left popliteal fossa for thirty-four years, and had been irregular in his attendance for treatment with the Finsen-Lomholt lamp. He responded moderately well (2+) to weekly local injections of 50–250 mg. of isoniazid but the spread of lupus at an uninjected site made oral treatment necessary. Improvement moderate (2+).

*Case G.*—Woman, aged 46. She had suffered from lupus for twenty-nine years. When first seen the two lesions in the region of the right knee had a superimposed dermatitis medicamentosa due to penicillin cream which had been used to control a secondary infection. When the dermatitis had subsided she was treated with isoniazid by mouth, 150–300 mg. daily. One of the lesions was also given local weekly injections of 100 mg. After twenty-nine weeks both lesions were rapidly clearing, more especially the one into which injections were given. An assessment of marked improvement was made (3+).

SUMMARY OF RESULTS

| | Oral | Local | Oral and local | Total |
|---|---|---|---|---|
| Cleared | — | — | — | — |
| Marked (3+) improvement | 3 | 1 | 1 | 5 |
| Moderate (2+) improvement | 1 | 4 | 2 | 7 |
| Slight (1+) improvement | 1 | — | 1 | 2 |
| No change | — | 1 | — | 1 |
| Total | 5 | 6 | 4 | 15 |

Local injections of comparatively small doses of isoniazid at weekly intervals produce clinical improvement which lags behind that achieved by oral therapy. A trial of daily injections has not been made because of patients' objections to daily visits to hospital but it might prove as valuable as oral treatment in selected cases.

We are now trying out a combined treatment by calciferol and isoniazid.

FIG. 1 (*Case B*).—31.3.52.

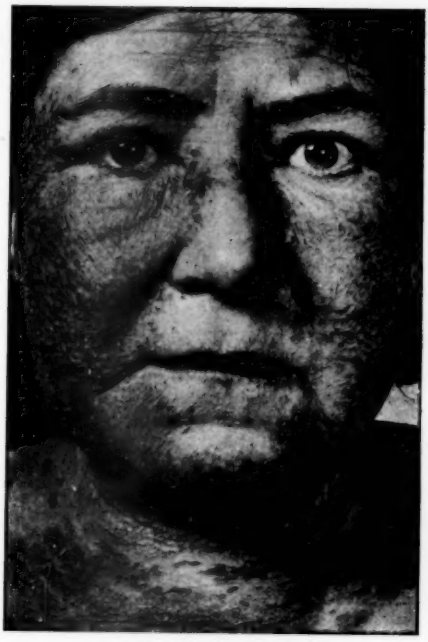

FIG. 2 (*Case B*).—10.6.52.

FIG. 3 (*Case B*).—12.8.52.

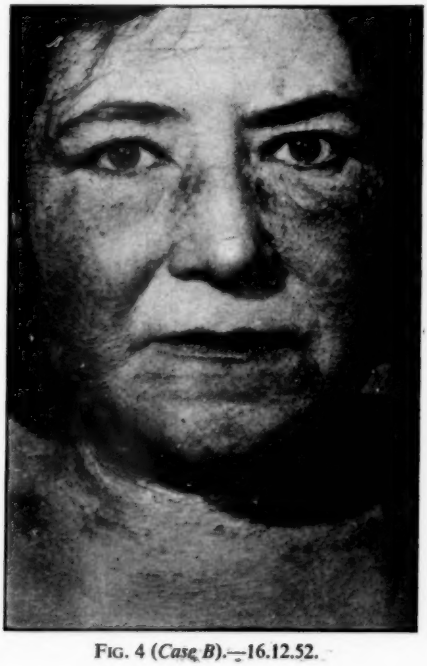

FIG. 4 (*Case B*).—16.12.52.

**Dr. J. Sommerville and Dr. J. A. Milne:**

*Report on 26 Cases*

**Dr. J. Sommerville:** I have treated 26 cases with isoniazid (250 mg. per day) for periods of from seven to thirty-two weeks.

In only 1 of these 26 cases was there a suspicion of pulmonary involvement, but subsequent X-ray findings disproved any activity. In reports so far published on the treatment of pulmonary tuberculosis with isoniazid the average number claimed as clinically cured is 25%; the M.R.C. report[1] confirms a distinct tendency in these cases to drug resistance, increasing from 11% at the end of the first month to 71% at the end of three months.

Of our 26 cases of skin tuberculosis not one has failed to show continued improvement: this apparent difference in response I am not able to explain. We claim 7 clinically cured and 8 almost so, the remainder showing varying degrees of progress.

*Toxic effects* have been noted in 5 cases; 3 suffered from menorrhagia, in 2 there was lassitude and loss of appetite, and 2 had polyuria; a few others showed increased appetite and one had an almost "pleasant sense of drunkenness".

Our results would seem to suggest that the drug is safe and efficacious.

Dr. John A. Milne, Lecturer on Skin Histopathology at Glasgow University, will report on the histopathological findings.

[Dr. Sommerville illustrated his remarks with photographs of 4 patients. Cases I and II had broken down again after improvement following calciferol, but after seventeen weeks' treatment with isoniazid they revealed no evidence of clinical activity (Case I, Figs. 1 and 2). The third had been refractory to light therapy, streptomycin, calciferol and Sulphetrone and the fourth had had no previous treatment; these 2 had improved markedly after nineteen weeks' and twenty-five weeks' treatment respectively.]

FIG. 1. FIG. 2.

FIGS. 1 and 2 (*Case I*).—Relapse after calciferol—Before and after nineteen weeks' isoniazid, 250 mg. daily.

**Dr. John A. Milne:** I have examined 14 of these cases histologically, 10 of which have been re-examined after varying periods of treatment. In all of them there has been evidence of regression of the lesion.

The first case illustrated by Dr. Sommerville shows a typical picture of lupus vulgaris before treatment (Fig. 3). Ten weeks after treatment (Fig. 4) shows a virtually normal skin, with a few areas of lymphocytic infiltration.

The third case, illustrated with facial lesion showed the typical histology of lupus before treatment. Fig. 5 shows the histology after nineteen weeks' treatment. The follicle has been replaced by a dense mass of lymphocytes with central giant cell of the Langerhans' type. This appearance is interesting and is in contradistinction to the picture of progressive transformation to "sarcoid" as obtained by the late Dr. W. Freudenthal in cases of lupus treated with calciferol. We hope to take further biopsies from this case.

[1] Medical Research Council (1952) *Brit. med. J.*, ii, 735.

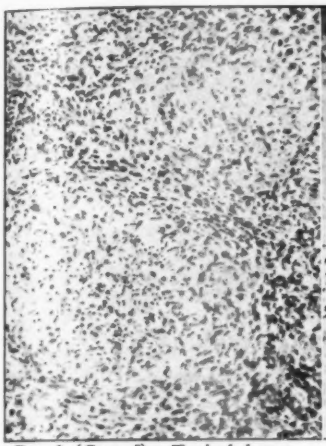

FIG. 3 (*Case I*).—Typical lupus vulgaris nodule before treatment. × 100.

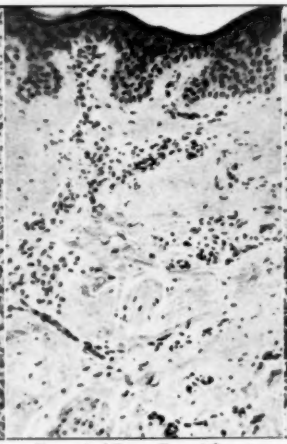

FIG. 4 (*Case I*).—After ten weeks' treatment complete disappearance of lupus tissue—Fibrosis with minimal infiltrate. × 100.

FIG. 5 (*Case III*).—After nineteen weeks' treatment (250 mg. daily)—Illustrates unusual finding of replacement of epithelioid cells by lymphocytes. × 100.

In the fourth case illustrated by Dr. Sommerville—a lady with extensive lesion of the forearm—a biopsy before treatment showed typical lupus vulgaris. Ten weeks after treatment a biopsy was taken from the periphery of the lesion where there were clinical signs of activity. The histological appearances were interesting. An area of rather hyaline necrosis was spreading out from the centre of the follicle and appeared to be destroying it. The significance of this change is not clear, but it is most unusual in lupus.

**Dr. G. A. Hodgson:** We have treated 8 or 10 cases of lupus vulgaris with isoniazid which have all improved but not as dramatically as the cases we have seen portrayed at this meeting. The most marked improvement was shown in a child of 5 who had had no previous treatment. In the older cases it was my impression that the lesions did move on Rimifon (Roche) (isoniazid) but they moved more quickly with Rimifon plus calciferol and I think there may be a case for giving Rimifon, calciferol and streptomycin all together.

**Dr. W. J. O'Donovan:** This exhibition of cases makes it plain that the fight against tuberculosis is proceeding among dermatologists as energetically as among general physicians.

For a quarter of a century I have been impressed, in the Lupus Department at the London Hospital, with the great difficulty of assessing progress and finality in cases under treatment. I would affirm that I had been seeing lupus daily for five years before I felt confident in suspending treatment and to this day I recognize the tubercle bacillus as so subtle an antagonist that I see such patients yearly.

I have seen patients that I thought cured before the 1939 war but when I returned afterwards to the Department some of these had relapsed.

Time is a great factor in the estimation of cure. Speed in clearance does not give one certainty. When a face has been marked by treatment with acids, by scraping and by X-ray treatment a warning of the persistence of lupus is given by the presence of a very fine scale. This implies congestion perhaps well below the malpighian layer.

If this be watched for six months there will appear a little, semi-translucent, bluish macule that needs treatment, or if left it becomes a recognizable early "apple-jelly" nodule.

**Dr. Louis Forman:** Isoniazid would appear to alter the skin reaction to the tubercle bacilli in the lupus granuloma. This may be more important than the antibiotic action. The bacilli are very scanty in lupus, almost impossible to demonstrate in sections, and difficult to culture. Again, we know that tubercle bacilli become resistant to isoniazid in about six weeks but lupus vulgaris continues to improve with the drug during the treatment time of four months. Great care should be taken to exclude any active lung infection when using isoniazid for lupus vulgaris, for the general physicians believe that streptomycin should be given as well so as to delay the development of drug resistance.

The incidence of toxicity to isoniazid appears to be low but not insignificant. Thus two reports

have described acute pellagra (McConnell, R. B., and Cheetham, H. D. (1952) *Lancet*, ii, 959) and confusional psychosis with residual organic cerebral impairment (Hunter, R. A. (1952) *Lancet*, ii, 960) following isoniazid treatment.

**The President:** The rate of progress of untreated lupus is determined by native and acquired resistance. Supposing that the cause, the tubercle bacillus, is even partially disposed of by chemotherapy, there is, I believe, no evidence that natural resistance is thereby lessened or any reason for supposing that it cannot continue to exert an effect even beyond the time of development of drug resistance. I feel strongly opposed to the view that because the disappearance of lupus from sight does not necessarily mean that it is permanently cured, therefore the new remedies are hardly worth trying. At the same time, I have always held to the view that local treatment remains an essential part of treatment.

The Treloar Hospital, Alton, has been equipped with Finsen and carbon arc lamps for many years; both here and at the Finsen Institute itself it has been admitted that until the advent of the new remedies, much widespread lupus could not be brought under control.

**Primary Systematized Amyloidosis.**—E. WADDINGTON, M.D., M.R.C.P.

Mrs. I. H., aged 57.

*History.*—Six years ago the patient had to cease playing the clarinet owing to increasing thickness of her lips and fingers. For the past five years she has suffered from fatigue and has become aware of her changed facial appearance. Three years ago she first noticed increasing breathlessness on exertion and during the last three months this has been severe and has been associated with swelling of the ankles. Two years ago her voice became husky. She has recently developed indigestion and flatulence and has had occasional attacks of diarrhœa.

*On examination.*—There is marked coarsening of the features, but no prognathism. The complexion is ruddy and the eyelids, lips and skin of the chin are thickened. The tongue is grossly enlarged and its movements are restricted. On palpation it has a rubbery consistency. The surface is normal. There are numerous purpuric spots on the chin and also on the buccal mucosa. The hands are broad and there is a doughy thickening of the skin on the medial and lateral aspects of the fingers. This infiltrated area is light brown in colour and semitranslucent. There are a number of ecchymoses on the surface. The feet show similar but less severe changes. There is bilateral chemosis and on the lateral aspect of the bulbar conjunctiva of the left eye there is a translucent nodule. (This lesion has been biopsied.) The heart is enlarged. The jugular vein is distended up to the angle of the jaw. There is œdema of the sacrum and ankles and crepitations at both lung bases. Blood pressure 200/130. The liver edge is palpable 1 in. below the costal margin. There is thickening of both ulnar nerves.

Urine: Albuminuria ++. Epithelial cells. Repeated examination showed no Bence-Jones protein.

*Investigations.*—Skiagrams of the skeleton (including pituitary fossa) showed no evidence of bone disease. Skiagram of the chest showed an increased transverse diameter of the heart with congestion of the lungs.

Electrocardiogram: a low voltage curve with ventricular extrasystoles. Blood examination showed no abnormality. Serum proteins 5·4, albumin 3·1, globulin 2·3%. B.M.R. + 10%. Plasma cholesterol 182 mg.%.

*Histology.*—(1) *Skin from side of finger*: The connective tissue of the dermis is largely replaced by a coarsely fibrillary material. In this material there are numerous clefts, some looking like artefacts, others, being lined by nuclei, resemble vascular spaces but the presence of intermediate forms indicates that they are all of the same origin. Scattered among the masses of fibrillary material are deposits of fibrin.

The staining reactions of the fibrillary material are as follows:

Eosin, Congo red intravitally, positive.
Van Gieson, Weigert's Elastic, Congo red in fixed tissues, negative.
Methyl violet, no metachromasia.
Reticulin, negative.

(2) *Nodule from conjunctiva.*—The biopsy shows similar changes to those in the skin. The appearances suggest that the "amyloid" material is an altered form of collagen rather than the deposition of any new substance. Morphologically it is unlike the material seen in true amyloidosis.

*Comment.*—Primary systematized amyloidosis may be distinguished from the more common form of secondary amyloidosis by the following features:

(1) It is not associated with chronic suppuration, granulomatous disease or rheumatoid arthritis.
(2) Metachromatic staining of the material is variable.
(3) The distribution of the amyloid is distinctive, with widespread involvement of muscle and small blood vessels. Particular features are macroglossia, gastro-intestinal and cutaneous infiltration and heart failure.

Our patient was admitted with severe hypertensive cardiac failure but in view of the changes in the electrocardiogram it is possible that amyloid infiltration of the cardiac muscle was a contributory

cause. Despite improvement in her cardiac condition, gross albuminuria persists suggesting similar involvement of the renal vessels.

The patient closely resembles the case reported by Wells, G. C. (1952, *Brit. J. Derm.*, **64,** 169). His patient also showed an abnormal serum beta globulin and an increase in plasma cells of the bone-marrow, without any evidence of bone destruction. Wells discusses the significance of these findings and suggests that this plasmocytosis is more likely to be a reactive phenomenon than a malignant myeloma. There is experimental evidence of a relationship between the production of antibodies and the number of plasma cells and this plasmocytosis of the bone-marrow, combined with an abnormal circulating globulin suggest that primary amyloidosis should be classified with the disorders of immunity.

My thanks are due to Dr. H. K. Goadby for permission to show this case.

**Borst-Jadassohn Intra-epidermal Epithelioma.**—H. HABER, M.D., and R. H. SEVILLE, M.D., M.R.C.P.

S. S., male, aged 39.

For the past two years this patient has had a slowly growing brown coloured papillomatous tumour on his left temple (Fig. 1). Clinically the lesion was like a seborrhœic wart, but biopsy was undertaken because it was fleshy and had a firm edge.

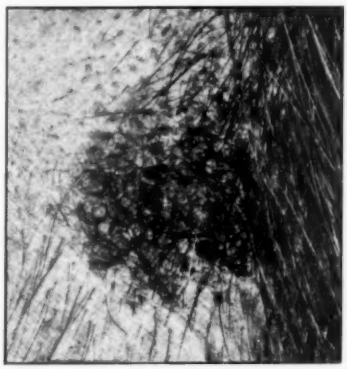

FIG. 1.—Papillomatous demarcated lesion of Borst-Jadassohn intra-epidermal epithelioma on the left temple. ×2.

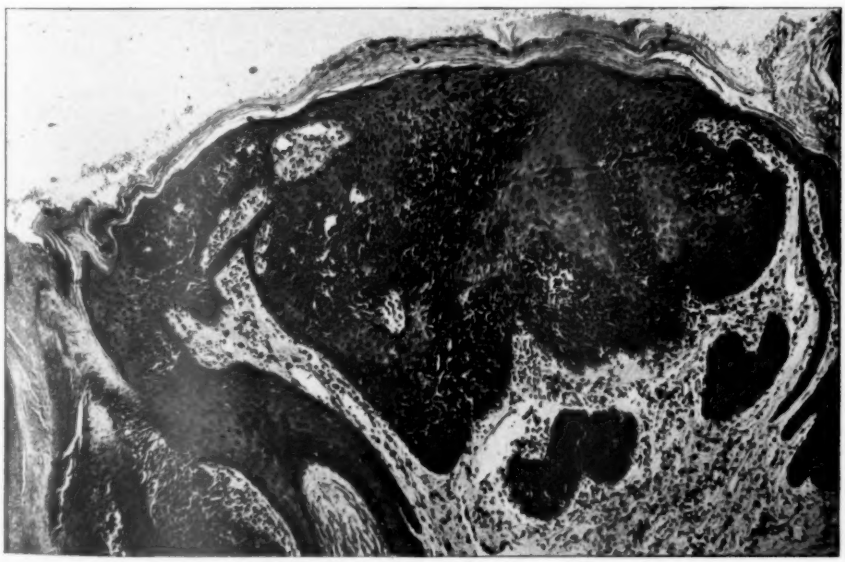

FIG. 2.—Intra-epidermal change. × 140.

*Histological section* shows a verrucose lesion that has been produced by an irregular hyperplasia of the epidermis which has changed its whole architecture. The stratum corneum is increased and shows areas of parakeratosis which correspond with absence of stratum granulosum in the same places. The stratum spinulosum shows two types of cells, darker staining spindle-shaped cells with a hyperchromatic nucleus exhibiting quite a number of mitotic figures. They are arranged in peculiar whorls. There is also intercellular œdema. The other type of cell shows homogenization of its protoplasm and a more eosinophilic staining producing a picture as if the stratum spinulosum has been replaced by a basal-cell and squamous-cell epithelioma of low grade. It is a rather bizarre histology not seen in any other intra-epidermal epithelioma. The tumour is sharply defined and the corium exhibits dilated blood vessels and a round-cell infiltration (Fig. 2).

**Dr. H. Haber:** There are several types of intra-epidermal epithelioma met with in dermatological histology, Bowen's disease, Paget's disease, erythroplasia of Queyrat and intra-epidermal basal-cell epithelioma. For the last two or three years I have come across lesions appearing as solitary warty papules or plaques of a peculiar appearance suggesting epidermal nævi, cellular nævi, seborrhœic warts or even melanomas. These could not be diagnosed clinically. The histology is of such a character that it must be regarded as a separate entity which was first described by Borst and forgotten but, later, attention was drawn to it by Jadassohn. The lesion in itself shows peculiar disarrangement of the architecture of the stratum malpighii with islands of spindle-shaped cells with prickles invading the epidermis with a tendency to form whorls. In some places squamous cells or premature hornified cells can be seen behaving in the same manner. There appear to be basal-cell epitheliomas or squamous-cell epitheliomas within the epidermis. I have not yet come across a lesion which has penetrated through the basal layer to invade the corium; so that one cannot say if this is a true intra-epidermal epithelioma or some peculiar nævogenic malformation within the epidermis.

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BORST, M. (1904) *Verh. dtsch. path. Ges.*, **7**, 118.
JADASSOHN, J. (1926) *Beitr. klin. Chir.*, **136**, 345.

The following cases were also shown:

**Trichostasis Spinulosa with Histological Features of Lichen Spinulosus.**—Dr. P. J. HARE.

**Vitiligo Treated with Mepacrine.**—Dr. J. S. PEGUM for Dr. P. J. HARE.

**Reticulo Granuloma.**—Dr. R. J. CAIRNS and Dr. H. HABER.

(1) **Necrobiosis Lipoidica (Non-diabetic Type) Treated by Excision and Grafting.** (2) **Case for Diagnosis. ? Dermatomyositis.**—Dr. H. BLACK, for Dr. G. B. MITCHELL-HEGGS.

**Granulomatosis Disciformis Progressiva et Chronica (Miescher).**—Dr. P. HALL-SMITH, for Dr. G. B. MITCHELL-HEGGS.

(These cases may be published later in the *British Journal of Dermatology*.)

# Section of Pathology

President—Professor G. PAYLING WRIGHT, D.M., F.R.C.P.

[*October* 21, 1952]

## Santiago Ramón y Cajal (1852-1934)

By W. H. MCMENEMEY, M.D.

THE scientist whose centenary we commemorate this year will be remembered not only as the greatest of neuro-anatomists, but also as a writer of distinction, a pathologist, a philosopher and a patriot. He secured for Spain a place of honour in a rapidly expanding world of medicine, establishing a school of histology which revolutionized the methods of approach to the problems of neuro-anatomy, and influenced the contemporary worlds of physiology and neuropathology. Civil war hastened the dissemination of his teachings, for many of his pupils scattered over the world to add their important quota to biology.

Cajal's father, Ramón, a resolute and energetic man, had had to content himself with the life of a non-qualified surgeon until such time as he could afford to complete his academic career: this he did when Santiago, the eldest of his five children, was already 6. Cajal's mother was a robust highlander who had known her husband since childhood.

The family left the isolated and impoverished village of Petilla in Aragon when Santiago was 2 years old, and two years later he went to school. His father, a profound believer in the sovereign will, also taught his little son, and the two would retire to the abandoned cave of a shepherd to avoid interruptions. At the age of 6 the bashful but intelligent Santiago became the amanuensis of the household and his father's secretary.

With a domineering and exacting father one understands why Cajal as a boy was wayward and secretive. A shy aloofness, in fact, dogged him throughout life. But he had a great respect for and fear of his sire. In fact he claimed to owe everything to the traits of character which he inherited from him.

When he was 8 the family moved to Ayerbe, where Santiago, who shunned the society of others, preferring to walk alone in order to enjoy the landscape and the flight of the birds, was mocked by the boys of the town. To this persecution he reacted by excelling them all in their diversions of stone throwing, pillage and robbery. Parental floggings, beginning with a whip and ending with cudgels and tongs, would inspire terror in him and his younger brother, a faithful partner in many a daring escapade. One wonders if Santiago's over-compensation had its origin in his father's endeavours to strangle a passion for sketching which was now beginning to assert itself. Ramón senior had no use for art so Santiago found it necessary to draw and colour in secret. At school he had an unenviable reputation for obstinacy and paid many visits to the mouse-infested dungeon where he discovered for himself the principle of the camera lucida.

At the age of 10 he was sent to the Scola Pia (Escolapios) at Jaca, but he was indolent and inattentive. In vain, he tells us, the energetic exhortations of Father Jacinto, who with furious blows from the strap and cat-o'-nine-tails made his case a matter of personal pride, failed to recall him to reality. "The blows sounded in my head", he wrote, "like those of the door knocker in an empty house." The disciplinary fasts and the repeated beatings upset his health and he was taken home. While convalescing under his mother's care he made gunpowder and a cannon, the first

discharge of which demolished a neighbour's gate and landed this student of ballistics in the town jail. The incident shows, I think, that he had acquired a facility for analysis and synthesis at an early age.

At the Institute of Huesca, where he is honoured as a past student, he continued his schooling, but a liking for the sport of Mars still pursued him. In his third year there he was able to report: "My ability with my fists and my skill in the use of the sling and the cudgel inspired respect in the bullies of the upper years." One day when pretending to work in his father's pigeon house, he found his way on to the roof of an adjoining confectioner and lo—on looking into an open garret window saw a library of books and a tempting display of candied fruits. With commendable judgment he avoided the sweetmeats but the volumes he proceeded to devour surreptitiously one by one. It was Robinson Crusoe which appealed to him most: "what a supreme triumph it must be to explore a virgin territory, to gaze upon scenes untouched by the hand of man . . . which seem created expressly for the discoverer as a reward for his outstanding heroism."

His father was worried. The uncontrolled imagination, the dilettantism and the bellicose tendencies of his first-born were not calculated to make him into a man of professional standing. He, therefore, apprenticed him to a barber, as he himself had been, so that, should all else fail, he would have a trade in his hands. And so the awkward and stubborn Santiago, with a longing to explore some primordial jungle, came to acquire skill with the razor. Next he was sent to a coarse and ruthless shoemaker of evil countenance who agreed to tame and harness his apprentice. But the vivid imagination of the introvert always took charge of a situation. "Whenever I had finished supper", he wrote, "I eagerly hastened to my little room and until I fell asleep spent my time giving form and life to the jumble of stains on the wall and the cobwebs of the ceiling which I transformed . . . into the wings of a magic stage, across which filed the cavalcade of my fantasies."

His martial ambitions received a setback when, as a boy, he witnessed the battle of Linas de Marcuella. The cries and groans of the wounded and the intensely white face of the dying general propped up on his horse taught him the terrible lesson of death. "What distressing indifference is that of nature", he wrote, "as it casts away . . . the masterpiece of creation, the sublime cerebral mirror, in which it acquires consciousness of itself." Fear would often grip the youth, in spite of his bravado. When he made his first train journey he panicked at the sight of the engine—"a hideous fire-belching mass of metal and coal . . . my alarm increased as I observed the disproportion between the size of the locomotive and the flimsy, rusty and disconnected rails, further weakend by rivets. . ." Paralysed with terror he refused to board the train but his colossal grandfather forced him into a carriage. An unusual reaction for a boy of 14, I think. Which of us at this age would be critical of the permanent way?

By now his father saw promise in his shoemaker son, so decided to interest him in osteology. He wanted to make him a surgeon rather than a physician "for", he said, "man bows only before crimson glory: a little blood heightens the splendour of the success, stamping it with the hall-mark of popularity." Together they climbed the walls of a cemetery by moonlight picking out from the shoal of bones half buried in gravel and nettles those which were most perfect. Although safe with his father fear laid hold of him: "I seemed to hear in the rattling of the bones protests . . . from the defunct."

The sullen Santiago, proficient now with razor and needle, was entered as a student at Zarogoza. About the same time his father was appointed a temporary professor of dissection. Father and son worked devotedly together. "There is no teacher more zealous than he who studies in order to instruct", wrote Cajal. But he still retained a passion for gymnastics, and for the sake of a comely young woman with blue eyes, with whom he was scarcely acquainted, he wellnigh choked a rival. Likening an athlete to a country with a large standing army he believed that excessive muscular development must lead inevitably to violence and bullying. One would have to be an angel, he wrote, to restrain in continual inactivity hypertrophic muscle fibres anxious for employment and justification. He absorbed the French romanticists and the thrills of Jules Verne. In fact he wrote the adventures of a microbe sailing on a red corpuscle to watch the epic struggles between leucocytes and parasites. Later this little germ found its way to the brain and discovered the secret of thought and of the voluntary impulse. How prophetic! Here was the desert island waiting for Robinson Cajal!

He saw army service in Cuba, showing promise as an administrator; but malaria and dysentery ruined his health and on his return from what proved to be a costly and futile campaign he saw many of his fellow patriots buried at sea. His cachexia and jaundice also lost him his betrothed and soon, to add to his misfortunes, he had a hæmoptysis, which needed all his father's skill and understanding to rectify. His disease must have been serious for he was dyspnœic, emaciated and profoundly depressed. He wrote of his convalescence: "one afternoon, seized with a fit of gloomy melancholy I scaled a lofty crest which I reached breathless and fainting . . . I conceived the plan of letting myself die with my face to the stars, far from men and with no witnesses other than the eagles nor shroud other than the approaching snows of autumn."

The sun, silence and art were his physicians and in fifteen months he was ready and eager to work for the regeneration of his country. His tool would be the microscope. Against the advice of his family and a priest the timid Santiago married a green-eyed golden-haired girl with "an air of

child-like innocence and melancholy resignation", after first satisfying himself that her psychological make-up was the complement of his own. From her he expected and received "soft obedience": to her he was always gallant and attentive.

In an attic which he equipped as a laboratory he spent what he called his honeymoon with his Verick microscope. He bought a simple Ranvier microtome and periodicals, mostly in French for he knew no German. In 1880 he wrote his first paper on inflammation in the mesentery, cornea and cartilage, illustrating it with his own lithographs. This prodigious worker wrote during his scientific lifetime 287 other monographs and papers besides 15 textbooks. Well has Dr. Courville called him the "Hercules of Histology". Referring to one strenuous bout of authorship Cajal said: "It was a delicious rapture, an irresistible enchantment." His reclusion now stood him in good stead. "Solitude creates for ourselves", he wrote, "the illusion of complete freedom."

An epidemic of cholera, which called for his help, almost tempted him into the exciting science of bacteriology, but he abandoned it on the grounds of economy. It required a whole Noah's Ark of propitiatory victims, he found, as well as a series of expensive gas incubators. He wrote: "I finally chose the cautious path of histology, the way of tranquil enjoyment. I knew well that I should never be able to drive through such a narrow path in a luxurious carriage." His devoted wife, with the care of a family which eventually increased to six, agreed to a proportion of his modest income being diverted for the purchase of glassware, reagents and periodicals, and even to the publication of a quarterly review.

From Zaragoza he moved to Valencia, Barcelona and finally to Madrid. Success accompanied him throughout and honours showered in upon him, not always to his liking, for, as he said: "Fame bruises while it caresses: it kisses, but it crushes." He became a national hero and was even offered a ministry of cabinet rank.

It was Don Luis Simarro, the psychiatrist of Valencia who, in 1887, demonstrated to Cajal in Madrid the methods of Golgi and Weigert-Pal. He could not sleep that night for excitement, for until then he had had to content himself with the cruder tinctorial methods in vogue or to make use of microdissection, not, however, without its fascination for the pupil of Robinson Crusoe. "What a triumph it was to clean from its neuroglial bramble thicket a cortical pyramid, that is the noble and enigmatic cell of thought."

In Valencia he worked in the post-mortem room classifying tumours and studying tissue reactions around them. He spent some of his happiest days in this city with congenial company at the cafés, which, however, it seems he attended more for self-discipline than choice. "It was necessary", he wrote, "to allot to each cell its rations and to each reasonable instinct a convenient opportunity for exercise." On Sundays he walked among the palms and the pines of the coast enjoying the *arroz* in the company of friends. Photography, chess and hypnotism were for a time his diversions.

1888 was his year of fortune. Working with embryonic material and with the aid of the procedure of double impregnation he was able to show that an axon could, by means of collateral and terminal branches, make contact with a variety of neurones. Later he deduced that the cell bodies and their processes took part in the chain of conduction, postulating the law of Dynamic Polarization, in which he generously gave part credit to Van Gehuchten. He rejected Gerlach's conception of the anastomotic network of nerve processes, an hypothesis defended by Meynert and Golgi and practically all neurologists. Instead he supported the "free ending" theory which had been advanced by His and by Forel. But transcendental problems faced him at each discovery. "What mysterious forces", he wrote, "precede the appearance of the nerve processes, promote their growth and ramifications, stimulate the corresponding migration of the cells and fibres in predetermined directions, as if in obedience to a skilfully arranged architectural plan, and finally establish those protoplasmic kisses, the intercellular articulations, which seem to constitute the final ecstasy of an epic love story?"

In the year 1903 he studied the neurofibrils; as the then-existing techniques of Bethe and Apáthy were inadequate he set his subconscious mind to work on the problem. The answer came to him in a flash as he was returning from a holiday in Italy: why not use hot silver nitrate? So preoccupied was he with his plans that he failed to enjoy the beautiful riviera scenery, but back in Madrid he "fell upon" his animals and his efforts were crowned with success.

In 1889 he journeyed to Berlin with his microscope and, speaking in French, demonstrated his preparations before the illustrious members of the Anatomical Society. The prejudice which he anticipated because he was a Spaniard did not materialize. Spain, he knew, had been known for artists, long-haired poets and gesticulating dancers, but not for scientists. He was well received, and Von Köllicker, who had visited Golgi two years earlier, now abandoned the reticular theory and went so far as to learn Spanish in order to read Cajal's earlier communications. He had many good friends in Germany. To Krause of Göttingen he owed his introduction into the scientific world, for this worthy published articles for him, paying for the chromolithographs himself; while to a chance recommendation of Virchow he owed his membership of the National Academy of Sciences in Madrid. On his way to Berlin Cajal called on Weigert, Edinger and Ehrlich and on his way back on his patron Krause, and Golgi: the latter, however, was not in Pavia but in Rome where his duties as

a senator had called him. Cajal met Golgi in Stockholm when they shared the Nobel Prize in 1906: he was at the station along with many others to meet the eminent Italian, his senior by nine years, but the friendliness which he had cause to expect was not forthcoming. Cajal, who was always punctilious in acknowledging his debt to the technique of his "illustrious colleague Golgi", had been accused by Golgi of not having given him credit for the discovery of the collaterals in the spinal cord. But he had published in an obscure provincial journal and it was not Cajal's fault that it was unknown to the world. At Stockholm Golgi chose to resurrect the defunct network theory and in so doing "made a display of pride and self-worship so immoderate that they produced a deplorable effect on the assembly." Cajal, who believed that the unsheathed sword in debate should be tipped with a bouquet of roses, says: "I was trembling with impatience as I saw that the most elementary respect for the conventions prevented me from offering a suitable and clear correction of so many odious errors and so many deliberate omissions." Separated in life they have been united in death—for they figure side by side on a medal recently struck in their honour.

Cajal was ill-at-ease in Stockholm; for prizes of this order, which cost him four months of his time in dealing with felicitations and follow-up ceremonies, one required, he said, "a heart of steel, the skin of an elephant and the stomach of a vulture." We can imagine the embarrassment of this diffident patriot when he learnt that the Prize for Peace was to be bestowed on Theodore Roosevelt. Cajal had, on the advice of his government, his friends and the Press, visited the United States only a few months after the war with Spain to take part in university celebrations at Worcester, Massachusetts. In America he disliked the women reporters. He did not really like women: like savages they suffered from an undue readiness to burst out laughing and in Southern climes they grew old too soon. Moreover, they wasted the precious time of the man of science, but he conceded that they were necessary. The wife, he said, is like the pack in battle—you can fight better without it, but what happens after the battle? He advised scientists to marry and to face up to the responsibilities of family life: the surest way to get women out of your mind, he argued, is to marry one of them. But he warned that only between the ages of 15 and 18 could a woman experience the emotion of real love, for only then is she free from ambition. The misfortunes of marriage, he held, had their origin in the fact that the woman does not choose but is chosen.

He visited England in 1894 in order to deliver the Croonian Lecture and stayed with the Sherringtons. The story is well known of how he locked his bedroom door so that the maidservant might not disturb the display of histological preparations which he had brought with him. It is said that his habit of airing his mattress from an upstairs window told the neighbours that a celebrity of unusual calibre was staying with the physiologist from St. Thomas's! Sherrington's description of him reveals a modest and simple man who in some respects was unusually naïve. He predicted the ultimate downfall of this country because of lack of industries, but his knowledge of England at that time was confined to what he could see from the continental boat train. At the Royal Society, presided over on this occasion by Sir John Lubbock, he was very nervous but was deeply moved when he saw the intertwined flags of Britain and Spain. He visited Oxford and Cambridge and returned to Madrid envious of our beautiful university cities.

But in Madrid he was happy; there he had friends in the *tertulia* of the Suizo café, and there he could walk on the banks of the Manzanares or in the parks where he would converse with acquaintances in humbler walks of life. But he closed his ears to the sound of the Siren of the capital. How easy was it for the bee to become a butterfly or even a drone! There was so much work to be done—the retina, both of man and insect, the synapses, the neuroglia and the comparative anatomy of the optic tracts, all craved his time. "My attention", he wrote, "hunted in the flower garden of the gray matter cells with delicate and elegant forms, the mysterious butterflies of the soul, the beating of whose wings may some day, who knows, clarify the secret of mental life."

He was of the sort who invites kindnesses. The Professor of Obstetrics gave his salary for the upkeep of the laboratory of which they were all so proud; the Professor of Surgery offered him a house, which it was not convenient for him to take. They made him Director of the National Institute of Hygiene and Biological Research, but the salary was reduced at his own request.

Short in stature and tending to stoop, he possessed broad shoulders and long arms. "His eyes were full and dark", said Sherrington, "lit or gloomed according to each mood." Cajal, this gifted and serious man, possessed, I think, all of what he styled the indispensable attributes of the researcher, namely mental independence, intellectual curiosity, perseverance, devotion to country and a desire for reputation. "'Tis from the sense you will find that knowledge comes", wrote Lucretius. Cajal was his own prosecutor rather than his own attorney.

He did not drink and did not smoke. In politics he was a democrat which suited, as he himself observed, his exaggerated individualism and his dislike for the principle of authority. The discipline of religion, however, he valued, "for", he said, "faith develops and leads to enjoyable longevity while doubt leads to pain in the soul and premature old age". The scientist, he held, as he contemplated the problems of Nature came near to the ideal of Henry James, of becoming a collaborator with God.

The aphorisms in his book *Charlas de café* reveal him as a cynic and pessimist imbued with a strong sense of justice and duty. He welcomed I think the principle of "the earth for all, talent for all" but

in 1910 he wrote: "will not the *aura mediocritas*, to which society aspires, enervate the mental faculties undermining the energy for scientific investigation? Will not collective capital be timid . . .? Will glory, the passion of philosophic and scientific genius, prosper in the grey and subdued atmosphere of the common weal?" But a time would come, he divined, when science would illumine the conscience and elevate the mind.

The First World War disheartened him. His dear friend, Van Gehuchten, had lost everything in the sacking of Louvain and was a refugee in England. He lost contact with all his colleagues abroad and felt isolated. "But", he said, "let us repel sadness, which is the mother of inaction: let us devote ourselves to life, which is energy, renovation and progress, and keep on working." "It is important", he wrote, "to put to use all our lucid moments, be it in meditation, which follows prolonged rest, or in the superintensive mental work which only the nerve cell heated by congestion can produce, or finally, in unforeseen intuition which frequently flies out, like a spark of steel, from the impact of scientific discussion."

Cajal was a kindly and inspiring teacher but he could be obstinate and even defiant. Once when a student threw orange peel he turned round from the blackboard and angrily offered to meet the culprit for a settlement outside the university precincts: at this time he would be close on 60. The sensitive and modest del Rio Hortega, whom it was my privilege to know, revered him like a father. In fact one saw the master mirrored in the pupil. They had the same diffidence, the same artistic and poetic sense, and in the formal gardens and intricate forests of the brain they satisfied their love of form and beauty and their thirst for adventure. Superb technicians, prodigious workers and lovers of Spanish culture, they had so much in common: Cajal influenced throughout life by his father; Hortega influenced by Cajal, although not of Cajal's wishing for he warned his pupils against extreme admiration of one's teacher. "It drains the personality and clouds the understanding", he said. An intriguing porter, resentful because the administrative strictness of Hortega had deprived him of certain perquisites, made trouble between them, misquoting to Cajal the words of Hortega in his lectures to students. Cajal, furious and insulting, ordered his junior to quit the Institute. Poor Don Pio, deeply wounded and weeping, did so. He did not return for several years until Cajal, acknowledging his own error in a happy way, invited his faithful assistant to demonstrate his excellent preparations. Don Pio imagined, I seem to recall, that his chief was a little jealous of his successful analysis of "the third element" of the brain.

Dr. Wilder Penfield and Don Pio on their last visit together found Don Santiago with a cold, propped up in bed surrounded by manuscripts. "Deafness and feebleness which had come on him recently were shutting doors behind him and the world, but his eyes blazed under shaggy brows showing an unquenched fire." He died peacefully in his eighty-third year while the great Cajal Institute on the hillside was under construction, a solid symbol of the renaissance of science in Spain.

"Cajal", wrote Sherrington, "reshaped our knowledge of the cellular architecture of the nervous system. He had, it is true, pulled down much, but he had built up more." For him the horizon of histology was limitless and all might share in the work and the satisfaction it gives. He wrote: "There await in the bosom of the living being millions of palpitating cells which, for the surrender of their secret and with it the halo of fame, demand only a clear and persistent intelligence to contemplate, admire and understand them." "Science so far from being exhausted, invites everyone with inexhaustible veins of ore." And for Britons he had a special word of encouragement for, he said, "grey matter goes with grey skies."

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# Section of Comparative Medicine

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## DISCUSSION ON PYELONEPHRITIS

**Dr. Reginald Lovell**, Royal Veterinary College, London: *Pyelonephritis in cattle due to* Corynebacterium renale.—A specific cystitis and pyelonephritis of cattle occurs in this and in other countries, and is diagnosed by the passage of turbid or blood-stained urine, and by the presence of *C. renale* in the urine.

Adult female cattle are the most frequent sufferers and both kidneys may be enlarged and palpable by rectal examination. The ureters are dilated and the walls thickened, and pus and tissue debris appear in the kidney pelvis (Figs. 1 and 2). The primary lesion appears to be in the kidney medulla and there may be an upward extension with grey patches of fibrosis in the cortex; some of the lobules are free. A cystitis may also be present and there is frequently an obstruction to the flow of urine with the development of a cavernous pyelonephritis. The early German workers (Ernst, 1905) collected and studied material from slaughter houses, and formed the opinion that the organism reached the kidneys by the blood stream. This view has been opposed by French and American students (Jones and Little, 1926), because of the frequency of the disease after pregnancy, and because of their inability to induce the disease in cattle by any other method than by the urethra; this method was not always successful, and a cystitis alone was produced.

FIG. 1.—Natural case of pyelonephritis in ox. Lobulated kidney shows some fibrosed areas on the surface and an enlarged dilated ureter containing tissue debris and *C. renale*; there is a constriction of the ureter below the dilated portion.

FIG. 2.—The cut surface of the kidney in Fig. 1; the lobulation corresponds to the calices and there is an atrophy of the renal substance; the renal pelvis as well as the ureter is dilated.

Older descriptions of *C. renale* described it as non-pathogenic for laboratory animals but we (Lovell, 1946; Lovell and Cotchin, 1946) have produced pyelonephritis in mice after intravenous inoculation of *C. renale*. About 20 millions of young viable bacteria kill a proportion of mice within a few days, and the changes in the kidneys are associated with the actual multiplication of *C. renale*; a cystitis occurs in some cases. The kidney lesion resembles that in natural cases in cattle, with the dilated renal pelvis, necrosis of the papilla and an inflammatory zone on its outer margin; there is a general absence of cortical involvement. Other routes of injection failed to induce such changes and our experiments with rabbits were less encouraging. Feenstra, Thorp and Gray (1949) gave many more than the 60 millions we injected and obtained lesions in the rabbit kidneys, similar to those in mice.

Efforts have been made to analyse the factors responsible for this tissue selectivity, and particular attention has been paid to the ammonia production by *C. renale*. The smell of ammonia in natural cases attracted the attention of early workers and the ability of *C. renale* to form ammonia from nitrogenous substrates is due largely to its urease activity. Uricase is also present in bacterial preparations and these observations, when extended, may lead to a closer understanding of the predilection of this organism for the portion of kidney with a high urea content (Lovell and Harvey, 1950). Further work on the action of extracts of *C. renale* and the production of a cortical ischæmia in experimental animals is in progress.

The epidemiological picture of the disease is beginning to form and bovine pyelonephritis should be regarded as a contagious disease with important subsidiary ætiological factors. *C. renale* has been recovered from the urinary tract of calves in an infected herd (Jones and Little, 1930), from the vagina of dairy cows (Weitz, 1947) and from the urine of cattle in infected and in non-infected herds (Morse, 1950). An apparent increase in the carrier rate in a dairy herd of 100 cows has been recorded; at the first examination 5 cows were detected and during the next fourteen months, 51 of the cows were carrying the organism on at least two occasions. The positions of the cows in their stalls suggested the spread from animal to animal, and Morse draws particular attention to the danger of the overt case. These animals are known to excrete the organism intermittently, and to show acute symptoms for short periods at frequent intervals. It is assumed that these exacerbations coincide with the development of the disease in other kidney lobules. The evidence points to the frequency of latent infections, which may be converted to frank cases of disease. This conversion may be conditioned by some factor associated with pregnancy, with some abnormality or obstruction in the urinary tract or with a retained placenta. Observations in the field suggest that these factors together with the specific organism cause the disease.

*C. renale* is sensitive to penicillin, and treatment with this drug has been adopted, but its success is problematical because of the extent of the kidney lesions.

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**Dr. S. De Navasquez:** *Experimental pyelonephritis in the rabbit.*—Before attempting to produce pyelonephritis, it was thought advisable to trace the path of non-pathogenic bacteria through the kidneys following intravenous injection in the rabbit, as the latter animal is readily catheterized, thus producing suitably sterile specimens. *Staphylococcus albus* and *Bacillus prodigiosus* were used as "tracer" organisms as these are comparable in size and shape to the common pathogens of the urinary tract, thus enabling one to assess the mechanical effects of these factors.

Following the intravenous injections of saline emulsions of these bacteria, unilateral nephrectomy was performed 15, 30, 60 and 120 minutes later. The excised kidney was incubated for eighteen hours at 37° C. and then examined for bacterial colonies.

Following a single intravenous injection, the excised kidney showed the bacteria still confined to the subcapsular and intertubular capillaries of the cortex up to fifteen minutes. Kidneys removed one hour later showed that the organisms had now passed lower down the capillaries, some 80% of the colonies being present in the capillaries of the medulla. Two hours later no bacteria were demonstrable in the kidneys, nor were bacteria present in the urine at any time. It may be concluded that non-pathogenic bacteria traverse the renal capillaries from above downwards and remain intravascular throughout their passage, which takes approximately two hours.

The same procedures were employed with *Staph. aureus* (Oxford strain and coagulase positive), *Escherichia coli* and *Ps. pyocyanea*, as these organisms are commonly responsible for renal and urinary

tract infections in man. Of these bacteria only *Staph. aureus* seemed capable of producing lesions. Both the bacilli passed through the renal blood vessels in two to three hours leaving no trace.

Within twenty-four hours of injection *Staph. aureus* produced a suppurative pyelonephritis with pyuria and pyrexia. Examination of the kidneys revealed focal abscesses extending from the cortex and converging through the medulla to the pelvis.

Microscopic examination of serial sections showed the presence of staphylococci in lesions, the nature of which provided the evidence whereby such organisms are capable firstly, of intravascular arrest, and, secondly, of producing tissue damage. The smallest and earliest lesions consisted of minute foci of closely packed staphylococci in rounded masses, for the most part still confined within capillaries and surrounded by cellular changes in glomeruli and tubules. These changes consisted of coagulative necrosis of all the cells in the immediate vicinity of the organisms. Although constituent cells of the part are still recognizable, their cytoplasm is opaque and the nuclei are pyknotic. There is, as yet, no inflammatory reaction and the lesion is clearly a pre-suppurative one consisting of a zone of coagulative necrosis. What has caused the arrest of the staphylococci in the capillaries? The large number of organisms in the centre of such lesions indicate that they have multiplied in situ over a period of some hours. These produce an enzyme coagulase which is capable of coagulating the fibrinogen of the plasma and thus each bacterial cell would, in fact, be covered by a layer of fibrin, thus enlarging its effective mass, like a rolling snowball. As the organisms multiply, more coagulase is produced which fixes them temporarily in a coagulated mass of plasma. This coagulation is not confined, however, to the plasma but may be seen in the surrounding parenchyma, due presumably to the diffusion of the enzyme. At this stage the staphylococci are locked in a solid mass of coagulated tissue which forms a barrier between them and wandering leucocytes. This pre-suppurative stage of initial necrosis is followed by autolysis and suppuration. The organisms are now free to be carried down the nephron through ruptured tubules, intertubular capillaries and lymphatics to reach the pelvis, producing a purulent pyelitis. The picture is now that of a purulent pyelonephritis, indistinguishable morphologically from that usually accepted as due to ascending infection.

By means of appropriate dosage it is possible to produce such pyelonephritis and yet allow the animals to survive. The diseased animals are pyrexial and lose weight for seven to ten days during which time there is pyuria. Clinical recovery occurs spontaneously and appears to be complete. At autopsy, however, the kidneys are found to be scarred. Such scars have the shape and size of the original abscesses and converge from cortex to medulla. Microscopically, they represent areas of replacement fibrosis in which varying amounts of tubular and glomerular tissue are embedded. Most of these elements are atrophied but in the vicinity of these scars may be seen glomeruli larger than normal and tubules which are distended. It is probable that these represent nephrons which are partially obstructed by the fibrosis, forming foci of intra-renal hydronephrosis. The similarity to human kidneys of so-called "arteriosclerosis" is striking. The focal distribution of these scars does not appear to reduce the functional capacity of the kidney, the affected animals surviving for as long as two years and more (De Navasquez, 1950).

It may be concluded that of the various organisms tested, coagulase-positive staphylococcus was the only one capable of producing pyelonephritis in the normal kidney of the rabbit.

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**Dr. J. B. Enticknap:** *Pathology of human chronic pyelonephritis* (Abridged).—The number of syndromes ascribed to chronic pyelonephritis has recently increased considerably. Among them are malignant hypertension (Saphir, 1952), renal salt loss (Enticknap, 1952), and renal osteodystrophy (Joiner and Thorne, 1953). Dr. Joiner and I also found it to account for 26% of 154 cases of chronic Bright's disease, 7 of 13 cases of uræmia of uncertain origin and a half of the cases in that series that were discovered incidentally at necropsy (Enticknap and Joiner, 1953). This communication describes the confirmation of the criteria used in making the histological diagnoses in the last three investigations cited and an assessment of the effect of this disease on the nephrons—for although interstitial changes are well recognized, gross destruction of glomeruli and tubules must be shown before one can accept that it causes extreme renal contraction. Most previous descriptions are based on necropsy material but nephrectomy specimens, which were employed here, offer many advantages: not only is the clinical diagnosis more certain in them and autolysis absent, but they also often show the early stages of the disease.

All specimens available for the years 1929–1952 were examined and those showing chronic inflammation were classified according to the predominating interstitial infiltration into three stages: (1) an active stage in which the infiltration was mainly composed of lymphocytes; (2) a healed stage in which fibrous tissue predominated, and (3) a healing stage in which the two were mixed. In addition the whole series was divided into two big groups: (1) 76 kidneys with chronic inflammation but no other disease, the simple group, and (2) 45 kidneys removed for nephrolithiasis or hydronephrosis. This last distinction was not, however, clear cut, for simple contraction often gave rise to some pelvic dilation. In accordance with modern usage the diagnosis of pyelonephritis, spelt without a hyphen, is

applied to the simple group. In this form it only implies co-existing inflammation of pelvis and kidney and not a pelvic form of nephritis.

As paraffin blocks only were available for many of the specimens most of the observations were made on hæmalum and eosin-stained sections, special stains being used when indicated. The individual lesions in the simple cases were compared quantitatively and qualitatively with those in the compound group and it may be said at once that the results were nearly identical. Since the lesions in the compound group were certainly due to chronic pyelonephritis, so therefore must have been those in the simple group.

Every case in this series had some interstitial abnormalities of characteristically irregular distribution but as these are well-established features of the disease I shall deal mainly with the changes in the nephrons. There were no cases of malignant nephrosclerosis nor was the diffuse benign form well developed in any of them.

*Severity of the disease.*—This was assessed in three ways:

(1) The thicknesses of cortex and medulla were measured on embedded material and the ratios between them calculated. The measurements of cortical thickness alone were found useful (Fig. 1), being reduced from a mean of 5 mm. in the active group to 3 mm. in the healing group. The mean thickness in the healed cases was only slightly less than in the active because the disease in these specimens was much less severe (*see below*). A cortical irregularity representing a macroscopic scar was present in 28% of these sections.

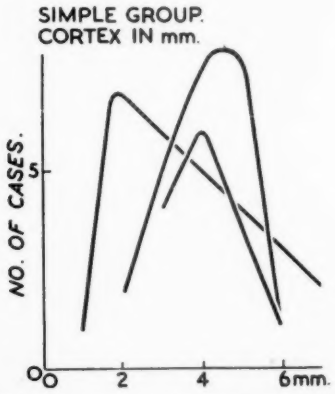


FIG. 1.—Mean cortical thicknesses in the three stages of chronic pyelonephritis shown on frequency distribution curves.

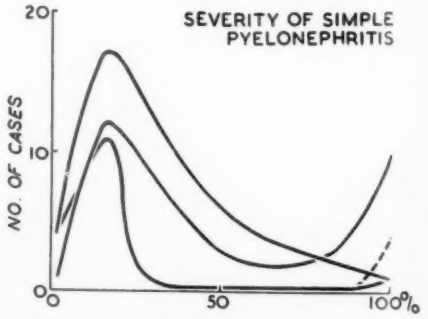


FIG. 2.—Similar curves for the severity of simple pyelonephritis.

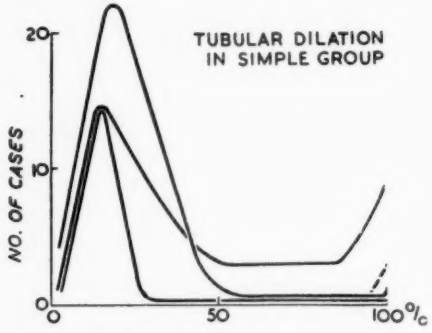


FIG. 3.—Similar curves for the amount of tubular dilation in simple pyelonephritis.

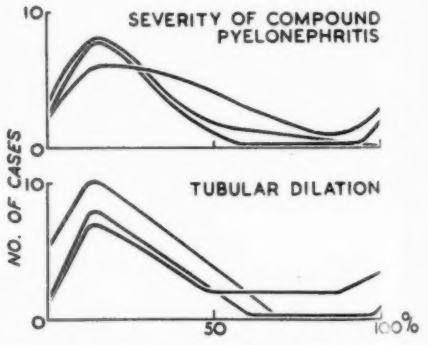


FIG. 4.—Similar curves to those in Figs. 2 and 3 but for compound pyelonephritis.

In all these four figures the highest peak represents the active cases, the middle peak represents the healing cases and the lowest peak those that are completely healed, reading from above downwards.

(2) The area of the section that contained inflammatory exudate was estimated, when it was found (Fig. 2) that active chronic pyelonephritis was not so extensive as the healing form and that, in most cases, if the disease had healed it had involved less renal tissue than if it was active. The presence of a secondary peak at the right-hand end of the curve representing active but healing cases, without a corresponding peak for completely healed cases, suggests, if one accepts that chronic inflammatory exudate does not disappear without trace, that healing of these former cases never results in restitution of recognizable renal tissue. This suggestion receives further support from the presence of the short interrupted line, representing 3 cases of "renal aplasia", placed here because I believe that they are cases of long-standing chronic interstitial inflammation. They are commonly called aplasias from their minute size (1–4 cm. in length) and absence of glomeruli, but both these features are completely consistent with their being the end-results of processes seen to some degree in every case of chronic pyelonephritis. The data from Fig. 2, the presence in the specimens of involuted large arteries and the histology of the fragments of the nephrons that do remain recognizable also support this belief.

(3) The amount of tubular dilation has been assessed in each case since this is the main effect of pyelonephritis on tubules that are not completely destroyed. The resulting frequency distribution curves closely resemble those relating to severity even to the disposition of the 3 cases of "aplasia" (Fig. 3).

Graphs of the same features in the compound cases (Fig. 4) show similarity even in detail, although the proportion of healed cases is slightly higher.

*Changes in the glomeruli.*—Some glomerular lesions were found in all except 2 cases and the number recognizable was reduced in 30% of the simple group and 42% of the compound; the difference is not significant and all subsequent figures relate to the simple group alone. They occur even quite early in the disease but, except when there is widespread interstitial infiltration, affect only a minority of the tufts. Most commonly (49% of cases) those affected were found in localized subcapsular areas and rather less often (33%) in radial wedges of granulation tissue. The majority had become fibrosed while epithelial changes (cubing, 9%; hyperplasia, 3%) were relatively uncommon. The lesion most frequently found is different at each of the three stages. In the chronic active cases periglomerular fibrosis was commonest (36% of cases); persistence of a few nuclei in a partially hyalinized tuft was

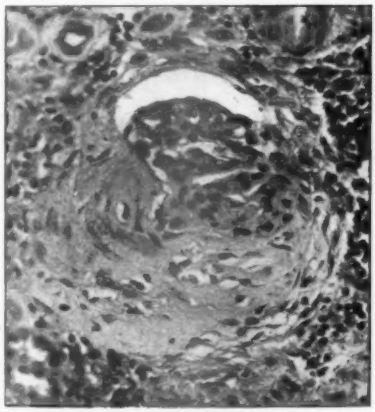

FIG. 5.—Partially hyalinized glomerulus; hæmalum and eosin. × 163.

FIG. 6.—Isolated colloid vesicles; phase contrast. × 192.

the characteristic lesion of the healing cases (67%); in the healed cases complete hyalinization was most frequently encountered (61%). This series suggests that contraction of interstitial periglomerular fibrous tissue causes glomerular atrophy, as does the appearance of the partially hyalinized glomeruli when stained by Van Gieson's method; they are then seen to consist of a dense peripheral band of collagen surrounding a looser central part in which nuclei are still recognizable. The boundary between the two components is quite sharp, suggesting that it is the basement membrane of Bowman's capsule.

Partially hyalinized glomeruli with segments of the tuft persisting (Fig. 5) were also commonest in the healing group (33%) although less common than those in which nuclei alone persisted. Very small tufts in dilated colloid-containing capsules showing endothelial cubing (Ellis, 1942) occurred in 37% of all cases, but there were never many of them in any one case. Various authors have stressed the diagnostic value of these two lesions but they were not, in this series, very helpful. Focal necroses were seen in 2 cases and glomerular hæmorrhages in only 3 others; this last is in marked contrast to the frequency of hæmorrhages in the interstitial tissue (Enticknap, 1953).

*Changes in the tubules.*—Of these the formation of numerous closely packed colloid-containing vesicles resembling thyroid acini is the most typical; these were found in 37% of cases at all stages, occasionally producing macroscopic cysts. The colloid spaces in this lesion are always roughly circular and it has been possible to show by the acid maceration method revived and recently described by Oliver *et al.* (1951) that this is because they are, in fact, vesicles (Fig. 6) and not tubules in continuity (Oliver, 1939). The same method shows, on the other hand, that the large convoluted spaces are dilated continuous tubules (Figs. 7 and 8). Many of them can be seen to form parts of aglomerular nephrons.

FIG. 7.—Ascending limb of Henle's loop; as in Fig. 6. × 192.

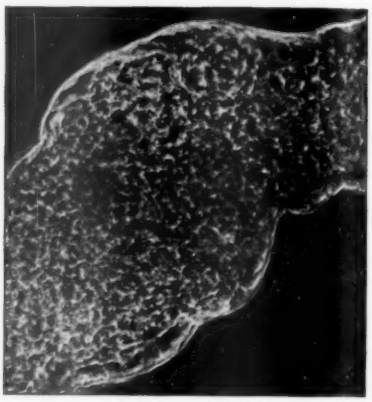

FIG. 8.—Ascending limb of Henle's loop from a case of chronic pyelonephritis; as in Fig. 6. × 192.

Slightly granular hyaline tubular inclusions were seen, mainly in the healed form (12%), and pus casts were seen only in the chronic active form (12%). Rarely a few calcified tubules were encountered (2%).

*Conclusion.*—This survey of more than a hundred kidneys in which the diagnosis of chronic pyelonephritis has been established beyond reasonable doubt has confirmed that the histological lesions in common use as diagnostic criteria do occur in this condition with considerable frequency. It has also shown that the disease varies in extent, that it may be very severe, that the severe cases probably do not heal—short of almost complete renal destruction—and that this renal destruction may be just as extensive as in any of the forms of glomerulonephritis.

This study forms part of a Survey of Bright's disease on which the author is engaged with Dr. C. L. Joiner at Guy's Hospital. Dr. Joiner is responsible for the clinical aspect of the investigation.

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# Section of Physical Medicine

President—DONALD WILSON, M.B., M.R.C.P.

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## DISCUSSION ON THE FUTURE ROLE OF OCCUPATIONAL THERAPY IN REHABILITATION

**Squadron Leader C. B. Wynn Parry:**

SUMMARY

The two kinds of occupational therapy—general and specific—are discussed.

Occupational therapy has distinct and different contributions to make in two classes of patients—those who will be fit to return to their former employment and those who will not.

These contributions are analysed in detail.

The establishment of remedial workshops where convalescent patients would do productive work is recommended.

The problems of the older age-groups are discussed, and the provision of geriatric workshops in industry is suggested.

The need for specialization in occupational therapy is stressed, and five main branches are suggested: diversional, psychological, rehabilitation, industry and in the home.

The goal of rehabilitation is to return the disabled patient to normal life, and the role of occupational therapy is the employment of practical methods in the attainment of this goal.

Occupational therapy has been divided into two main classes—diversional or general, and remedial or specific.

Diversional therapy has its greatest scope for the patient confined to bed in hospital. It makes a definite positive contribution by taking the patient's mind off his disease or injury, relieving tedium and preparing the ground for later and more active rehabilitation. It should be designed when possible to aid his physical recovery by keeping unused muscles fit and promoting the blood circulation. It can also be devised to have a remedial object—for example, the restoration of shoulder movements after thoracoplasty and injuries to the forearm. It should not produce bad postural habits and for this reason it is questionable whether knitting is a pastime to be encouraged in bed. The prescribed occupational therapy must be of interest to the patient and should, whenever possible, open up new avenues of activity leading either to financial gain or to permanent hobbies.

This diversional aspect of occupational therapy is capable of a clear positive effect and could be considerably developed to advantage to cover wider and more practical occupations.

Remedial occupational therapy has its greatest scope during convalescence—when the patient is no longer confined to bed but has not returned to work. The adjective remedial is here used in its widest sense and includes specific techniques to restore physical function, vocational and work assessment, and, where necessary, vocational training.

The first essential is to make an accurate prognosis of the patient's ability to return to his former occupation. It is vital that this decision is taken as early on in treatment as possible so that the patient is settled in his mind and can take full advantage of rehabilitation. Research is much needed into techniques of physical medicine that will enable more accurate prognosis to be made.

Techniques of occupational therapy undoubtedly accelerate the rate of recovery of joint movement after fractures and dislocations, and furthermore the end-result is often far better. Mead and Harell (1950) state that occupational therapy is better suited to gains in endurance, tolerance, co-ordination and dexterity than in the increase in muscle strength and joint range. They conclude that occupational therapy is most suited to disabilities of hands and fingers and is unsuitable for building up maximum muscle power or increasing the range of large joints. We have found at the Medical Rehabilitation Unit, Chessington, that while occupational therapy techniques are the only really effective way of treating hand and finger disabilities, they are also more effective than simple remedial exercises in restoring the function of certain larger joints. In the Vauxhall Rehabilitation

Shop, for example, machines are modified to increase the range of movement and power of muscles controlling practically every joint in the body. To resolve this obvious difference of opinion, we need much more detailed information on the likely end-result and probable duration of disability in fractures, dislocations and following orthopædic operations, and on the treatment of choice for each disability—in fact, clinical research with a view to a more scientific use of the occupational therapy department.

Occupational therapy has distinct and slightly different contributions to make in the rehabilitation of the two main classes of patient, those who will be fit to return to their previous employment and those who will not.

For the severely disabled patient who is unable to return to his previous employment the first essential is to learn to perform independently his own daily activities. The recovery of independent personal care improves the patient's morale immeasurably, it releases another person from having to care for him and it prepares the ground for future specific remedial therapy.

If the patient is so severely disabled as to be unable to perform certain daily activities by himself, the occupational therapist can devise suitable gadgets to overcome the disability, such as were demonstrated by Cooksey at the International Congress of Physical Medicine (1952). Many of these appliances have to be made especially for individual cases and are unlikely to be commercially manufactured, and it must, then, be the occupational therapist's responsibility to devise and make them. Where possible the patients could make such appliances for themselves or for each other and the range might be extended to include splints and special surgical appliances.

Having taught the patient to cope with his daily activities and devised suitable gadgets or splints to complete this aim, the next step is the provision of specific remedial occupational therapy. This should be either directly related to the patient's future occupation or devised to assist the therapist in an assessment of the patient's abilities.

Covalt (1952) has stressed the valuable contribution an occupational therapist can make towards satisfactory resettlement by assessing such abilities as accuracy, speed at work, concentration, ability to follow instructions, neatness, initiative, stamina, work tolerance and handling of tools. She can further help the patient to discover for himself his latent capabilities and potentialities for training, by practical aptitude testing. Resettlement can then be effected at the earliest possible stage in rehabilitation and training for a future occupation can proceed *pari passu* with physical and mental recovery. Thus not only does the patient save a great deal of time but the doctor can then fill in the D.P.I. form with considerable accuracy.

At the R.A.F. Medical Rehabilitation Unit, Chessington, we have developed a resettlement scheme for disabled patients who have to be invalided. As soon as it is clear that the patient will not be fit to remain in the Service, resettlement is started, even though treatment may continue for several months. The patient is asked to attend the resettlement clinic. These clinics are held weekly. The Medical Officer outlines the medical aspects of the case and the patient's service and civilian industrial history. The occupational therapist discusses his capabilities, and assesses the type of work most suited to the patient's physical and intellectual abilities. The Education Officer contributes details of any tests carried out and describes any educational course that he considers would be desirable. The D.R.O. (Disablement Resettlement Officer) then investigates the various aspects of the particular trade chosen, such as the employment position in his home area, details of training courses and contacts with local firms.

Through the kindness of the Regional Office of the Ministry of Labour, arrangements have been made for patients from Chessington to attend the Government Training Centre, Waddon, for a trial period of work. We use this form of occupational therapy in two main ways—first the instructor at the centre gives the patient a practical test in his chosen trade, and decides whether the patient is physically and temperamentally fit for the job. The patient in his turn has the opportunity of seeing the actual job at first hand and can decide if he likes it. Should the result of this trial period be unfavourable, other channels are immediately explored and thus the minimum of time is wasted. This practical trial is the only method of proving to the patient that the choice is right or wrong.

Secondly, when a suitable trade has been chosen the patient attends the Centre for part-time training, thus combining physical rehabilitation with resettlement and providing a gradual transition from convalescence to full working conditions. It allows the patient time to gain confidence and reduces failures of resettlement to a minimum. For those patients for whom Technical Trade resettlement is inappropriate, there are education classes, part-time training at Technical colleges, or correspondence courses. In certain cases the occupational therapy department can offer both remedial therapy and, concurrently, part-time training or refresher courses. Certain local employers within easy reach of the Unit have also kindly offered part-time training facilities.

Since this scheme started, some 150 patients have been resettled on these lines and we have had only two failures to date—one in a patient with poliomyelitis who prematurely terminated his training at a Government Training Centre for domestic reasons and one patient with bilateral amputation of the legs who is now busily engaged in a Turf Accountant's Office, a form of resettlement upon which the patient and his Medical Officer had a difference of opinion.

The problems encountered in the services are somewhat different from those in civilian life—the age groups are different and there are certain advantages of the Resident Rehabilitation Unit which make resettlement easier. But from our experience of occupational therapy in rehabilitation I should like to suggest some lines on which occupational therapy might develop in the future.

We have been forcibly impressed by the truth of Licht's dictum (1947) "Occupational therapy which does not provide present financial returns or contribute to future vocational placement is almost certain to be useless".

The next contribution of occupational therapy to be considered is in the patient who will be fit to return to his former occupation but is off work while undergoing rehabilitation. This problem has been brilliantly solved by some large industrial firms such as Vauxhalls and Austins where patients carry out productive paid work in the Rehabilitation Shop on machines designed to suit the disability and provide remedial treatment. Such schemes, however, are not practical in the cases of small firms.

The number of people absent at any time in one particular large industrial concern has been estimated at 2½%. A rough estimate of the number of the working population off sick at any time and capable of some form of productive employment suitably devised for the disabilities concerned cannot be less than 100,000.

There is a strong case for productive paid work during rehabilitation for three main reasons: firstly, long periods off work represent an economic burden on the community, secondly, patients recover more quickly if there is a financial incentive and thirdly, the whole family's morale suffers from the wage earner being idle.

The Tomlinson Report (1943) states that where properly graduated light employment in industry cannot be provided during convalescence, it would be far better for light employment on productive work under non-competitive conditions and adequate medical supervision to be provided in special centres. Such a scheme has been adopted at the Luton and Dunstable Occupational Therapy Department, where local firms supply the materials for productive work. The work is designed on a remedial basis for the recovery of specific physical function and for the return to working conditions as early on in rehabilitation as possible.

Such centres could be developed all over the country. As soon as a patient is fit to leave hospital he would enter the occupational therapy workshop and spend increasing periods of the day on productive paid work, the materials for which would be supplied by local firms. The workshop should be situated within easy reach both of the hospital and local industries. Where possible the work should be designed to be both productive and remedial. When this is not possible, it is submitted that some form of productive employment has considerable advantages over enforced idleness. The occupational therapist's responsibilities in such a workshop would be the adaptation of machines and crafts to suit specific disabilities, checking individual patient's progress both in joint range and muscle power and in work ability, and in the early establishment of a prognosis with the physical medicine specialist's collaboration. Possibly the department could combine the specific remedial and paid productive workshop with the work assessment of the patient unfit from the outset to return to his previous work. Many of the latter cases would benefit more from special Rehabilitation Units where the rehabilitation of severely disabled patients is a full-time job and there is much to be said for segregating the minor disabilities from the severely disabled.

Such a scheme means that the occupational therapist must be more familiar with the techniques and problems of industry, though this is surely an essential development at a time when economy is paramount and a realistic approach vital.

Finally, the function of the occupational therapist in industry could cover three main aspects.

First, by liaison with the occupational therapists in the rehabilitation workshops, she would be responsible for the proper placing of patients discharged back to work in suitable employment, because of her specialized knowledge of applied muscle physiology and industrial and craft job analysis. Early consultation between the industrial occupational therapist, rehabilitation occupational therapist and specialist in charge of the patient would result in correct placing, thus aiding the employer in knowing the future career of his employee and offering security to the patient.

Secondly, she could do much towards prevention of disease or injury at work by studying correct working positions, detailed job analysis and muscle and joint function in a variety of movements and occupations. Business efficiency experts are agreed that there is a definite place in industry for someone who can first assess by aptitude testing the right man for the job and who can apply a knowledge of kinesiology, fatigue and movement patterns to the problems of the most efficient manner of performing individual tasks both for increased production and prevention of breakdown.

Thirdly, she would be in charge of a geriatric workshop. It is common knowledge that the average age of the population is increasing rapidly, and also that old people are fully capable of productive work long after retiring age. Welford (1950), in his book "Skill and Age", found that although older people found it harder to master new problems, their work was more accurate than the younger groups with only a small loss in speed. Their concentration was also greater. In the future the problems of the older men and women will become increasingly grave, and if they are not engaged in some form of productive employment the economic burden of the community will

be considerably increased—also the majority of older people are much happier working. There is a case for the provision of small geriatric workshops as an integral part of the main factory where older people carry out suitable work with agreed financial reward. An occupational therapist with special knowledge of industrial techniques and the problems of the older age groups would be the ideal person to supervise such workshops.

There would seem to be a place for specialization in occupational therapy in five main branches: first, for the patient in bed comprising practical diversional therapy; second, psychiatric occupational therapy which has a contribution of immense importance to make; third, in the home, including the study of methods to lighten the burden of the disabled housewife; fourth, in rehabilitation, for obtaining maximum recovery possible and assessing the patient's work abilities, and fifth, occupational therapy in rehabilitation workshops and in industrial concerns.

There is scope for research into such problems as the analysis of muscle function in health and disease, the study of trick movements, motion patterns and the best techniques for accelerating recovery in particular injuries and diseases.

There is also scope for the occupational therapist to solve many of the problems in industry for the prevention of injury and breakdown.

Above all, the occupational therapist can help the patient to realize his full potentialities and can assist him to resume his place as speedily and efficiently as possible in his normal economic environment.

ACKNOWLEDGMENTS

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I wish to thank our occupational therapists, Miss N. Smyth and Miss J. Cumberland, for their suggestions and criticisms.

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**Miss G. Thornely:**

SUMMARY

Occupational therapy is most effective when started at the right moment; that is, as soon as the patient is medically fit or over the shock of the injury or operation. Treatment should then be continuous until the patient is living his normal life. Occupational therapy has an important economic role in the National Health Service. It accelerates the rate of recovery, and shortens the time of treatment between injury and return to employment. Many hospitals still have no occupational therapy departments and many departments still remain to be developed. This is obviously a short-sighted policy—weeks of disablement and sick benefit are paid out by the Ministry of National Insurance which might be saved through better facilities of rehabilitation. The Industrial Rehabilitation Units cannot take the place of the hospital department and in some districts there is a gap between these Units.

The co-ordination between brain and limb is frequently lost after injury because of shock and lack of early movement. It is, therefore, essential that use is resumed at the very earliest, not only to retain mobility to all sound joints, to increase circulation and accelerate healing, but to maintain cortical pattern. More patients should be sent early to the occupational therapy department, and not, as is so frequently the case now, when there is inco-ordination, or bad habits of movement. These, of course, prolong disability.

Occupational therapy for hand cases is the ideal treatment because of the fine movements required by skilled workers. It also helps considerably in the recovery of movement and power of large joints.

The scope of occupational therapy is broad and ill-defined—broad, because it uses any activity (outside those already used by other ancillary services in the hospital) which will help the patient regain maximum health and ability. It must remain broad because the treatment must be suitable to the disease or injury, the personality or calling and the ultimate mode of life of the patient. It is ill-defined because as a recognized method of rehabilitation it is comparatively young and is still developing.

This development depends on several unpredictable forces. The economic influence is one of those which most affect the development of occupational therapy within the National Health Service. This development also depends on the training given to occupational therapists, a question which is at present under review. The Syllabus presents a problem as to its scope and content in order to ensure sufficient theoretical knowledge and breadth of practical subjects to meet demands.

Moreover, much of the present equipment is unsuitable. I hope that before long specially designed apparatus will be produced for occupational therapy departments.

In the past few years there has been development in the use of industrial work for rehabilitation, as practised by Austins, Vauxhalls and the Luton and Dunstable Hospital. No occupational therapist is employed, but a surgeon gives directions for treatment to the technicians in charge of the workshops, weekly. There are occupational therapists interested, anxious and capable of work in industrial departments, who, by receiving the necessary prescription from the surgeon, would relieve him of the detailed direction of treatment. There are many patients in industrial areas who would benefit from this type of rehabilitation—though there are still others for whom light crafts and creative work would provide greater benefit.

During rehabilitation, as at work, the patient must have one of four incentives: first, remuneration, monetary or in kind; second, the incentive of possession—in most departments the patient is encouraged to buy what he has made; third, the incentive of increased self-confidence when he is able to demonstrate to himself and to his friends his capacity for creative work; lastly, the feeling of being of help to others, i.e. in making appliances, splints and other items for the use of other patients. When the patient's own initiative and ability are stimulated in this way, he is provided with a useful hobby for his leisure hours.

Hospital rehabilitation departments thus undertake the treatment of the severely disabled patient so that he may be fit enough to take up sheltered employment in the factory or workshop, or special work in the home.

The occupational therapist who is interested in her patients will provide the various small aids which do so much to make life tolerable for the badly handicapped or the chronic sick. Special instruments to help him in his toilet and to enable him to eat by himself can all go a long way in restoring his morale and in giving him a brighter outlook on life, and incidentally, in easing the nursing responsibilities for relatives.

Occupational therapy may be more used in the future to help old people to retain or regain function and activity. Many of these patients have been long in hospital and have deteriorated considerably. They have lost touch with their families or have no relatives, and have ceased to have any interest in life. Rehabilitation would often enable them to leave hospital and to live in an old people's home or hostel, where their maintenance would be less expensive. This would also release hospital beds for acute cases.

I should like to see the institution of ex-patient clubs run on the lines of Darby and Joan clubs, but for all ages. Here the chronically sick and disabled could find recreation, occupation and companionship. The visit of an occupational therapist at regular intervals to these clubs would be of value both in ensuring maintenance of improvement and in supplying aids and appliances for their use.

It is not possible here to discuss the part which occupational therapy may play in the future in the treatment of the psychiatric patient or the tuberculous.

There is a tendency at present to split up the occupational therapist's work into sections of art, music, recreation, social and educational therapy. All these sections should be co-ordinated by the occupational therapist. This is important because some therapists attend only part-time, and may not have the necessary medical knowledge or special knowledge of the patient required to ensure correct treatment.

There may possibly be a call, in the future, for occupational therapy in Remand Homes, Borstal Institutions and Prisons where this treatment could help in the rehabilitation of the inmates.

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# Section of Neurology

President—MACDONALD CRITCHLEY, M.D., F.R.C.P.

[*November* 6, 1952]

MEETING HELD AT THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W.C.1

## Chronic Changes in the Central Nervous System following Thorotrast Ventriculography

By ROBERT HUGHES, M.D., M.R.C.P.

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SINCE it was first introduced by Bluhbaum, Frik and Kalkbrenner (1928) Thorotrast has been used as a contrast medium for a variety of diagnostic radiological procedures. This preparation is a colloidal suspension of thorium dioxide; when introduced into the blood stream it is taken up by the reticulo-endothelial system (particularly the spleen, liver, bone-marrow and lungs) and is retained permanently within the body; little or no excretion appears to take place.

As Martland and Humphries (1929) had described the occurrence of malignant disease in dial painters using luminous paint containing radium and mesothorium, almost from the first the advisability of injecting a radioactive substance such as Thorotrast was questioned and an extensive literature rapidly appeared citing the advantages and disadvantages of this material. With experimental animals, toxic effects due to the radioactivity of Thorotrast were easily demonstrated but these have proved comparatively uncommon in man as Thorotrast has usually been used in the diagnosis of conditions which later proved fatal. Sarcoma of the liver following Thorotrast injection was described by MacMahon, Murphy and Bates (1947), marrow aplasia by Schmitt, Schulte and Lapp (1950) and carcinoma of the lung by Abrahamson, O'Connor and Abrahamson (1950). It would seem likely that some of the early toxic effects may be mechanical in origin or due to the toxicity of the heavy metal. If any of the material leaks into the subcutaneous tissues there is usually considerable pain and a large mass of fibrous tissue forms in which are numerous phagocytes containing Thorotrast; such cases have been reported by Ziffren (1940) and Schumann (1943). Whitaker, Davie and Murgatroyd (1933) described cloudy swelling of the liver cells shortly after Thorotrast was injected intravenously. In 1932 the Council on Pharmacy and Chemistry of the American Medical Association decided against the intravenous use of the drug in the larger dosage necessary for visualization of the liver and spleen.

In the field of neurology and neurosurgery Thorotrast has played a most important part; Moniz used this substance almost exclusively in the development of cerebral angiography. It was first introduced into the subarachnoid space by Radovici and Meller (1932); in this country Twining and Rowbotham (1935) described a method of using both air and Thorotrast to outline the cerebral ventricles but this technique was soon abandoned owing to the aseptic meningeal reaction which frequently followed.

In the following case Thorotrast had been injected into the cerebral ventricles for radiological purposes, there was no immediate toxic reaction but thirteen years later evidence of neurological damage became apparent. I have not been able to discover any similar case in the literature.

The patient was a male who in 1938 was aged 22 years.

He at this time reported to an ophthalmologist with headaches of three months' duration and was found to have a mild bilateral papillœdema (R. 1½ D, L. 2½ D). He was then referred to a neurological clinic for further investigations; clinical examination showed no other evidence of neurological damage and other systems were normal. Skull X-ray normal. Blood W.R. negative. C.S.F. normal (except for some red blood cells). Air encephalogram was reported as showing some displacement of the frontal horns of both ventricles to the right side. On 28.3.38 a Thorotrast ventriculogram was carried out, 5 c.c. of Thorotrast being injected into the lateral ventricle (the side into which the injection was made is uncertain); it was again reported that the ventricular system was displaced to the right side. On the following day the patient's temperature increased to 101·4° F. but no other toxic effect was noted.

Although a diagnosis of intracranial tumour was made, for some reason which is not clear no surgical procedure was attempted. He was discharged from the hospital on 11.4.38 and kept under observation in the out-patient department up to 5.7.38; it was then noted that he had not been vomiting during the past two weeks, the headaches had improved, the changes in the discs had improved but they were not yet normal.

On 22.11.38 the patient was seen as an out-patient at another hospital in the area; he was still complaining of headaches and vomiting, the left disc was still blurred but no other abnormality could be found.

The patient returned to his usual occupation as a tailor's presser and over the succeeding months his headaches gradually subsided. He served in the Army from 1940–48. He served in India for five years and was finally discharged in Medical Category A 1 with the rank of W.O.2.

On 14.8.51 patient reported to the Neurological Clinic at the Royal Southern Hospital, Liverpool, complaining that for four months he had noticed urinary frequency, incontinence after taking large quantities of fluid and nocturnal enuresis. He complained of slight swelling of the lower abdomen and slight numbness of the left buttock. There was no disturbance of the sexual functions.

On examination, it was found that he had a low cauda equina lesion; there was complete loss of all forms of superficial sensation in the fourth sacral segment and below, the anal canal was patulous, anal sensation was lost and three fingers could be inserted into the anus without causing discomfort. The anal and bulbocavernosus reflexes were lost. The bladder was distended to the umbilicus. No other abnormality was found in the nervous system. The lungs and heart were normal. The blood pressure was 130/80.

The patient was admitted to the hospital and a suprapubic catheter was inserted as an emergency measure. Microscopical examination showed that he had a *B. coli* urinary infection; this was treated with a sulphonamide compound.

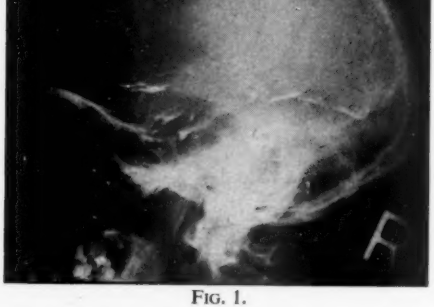

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 1.—Lateral X-ray of the skull showing Thorotrast still remaining within the cranium.

FIGS. 2 and 3.—Lateral and A.P. air-encephalogram showing a moderate degree of symmetrical hydrocephalus involving the lateral ventricles. The Thorotrast is seen to be present in the more dependent parts of the lateral ventricles.

FIGS. 4 and 5.—Lateral and A. P. views of the lumbo-sacral region of the spine. These show the Thorotrast outlining the lower part of the dural sac and a small pool of Thorotrast at the extreme lower part of the spinal theca.

On X-ray of the skull it was found that some Thorotrast still remained within the cranium and on air encephalography this was found to be in the more dependent parts of the lateral ventricles, largely on the floor of the anterior horns, bodies and posterior horns. The air picture showed a moderate degree of symmetrical hydrocephalus involving the lateral and third ventricles. X-ray of the lumbo-sacral region of the spine showed that there was also a small pool of Thorotrast at the lower end of the spinal theca and that in addition the dye had formed a thin layer over the dura for several inches above this (*see* Figs. 1 to 5).

On lumbar puncture the C.S.F. pressure was 70 mm. and there was a normal response to jugular compression. The fluid contained 3 red cells and 1 white cell per c.mm., 100 mg.% protein; there was no increase in globulin; Lange curve 1110000000. The Wassermann reaction was negative in both blood and C.S.F. Serum non-protein nitrogen 30 mg.% Chest X-ray normal.

A cystoscopy was performed by Mr. Cosbie Ross, and rigidity, bullous œdema and induration of the bladder neck and base of the bladder were found. There was some trabeculation and a tendency to median bar formation. A cysto-urethrogram showed narrowing of the prostatic urethra, especially in the region of the internal sphincter. Resection of the bladder neck was carried out with a cold punch.

The patient was discharged from hospital on 26.10.51 at which time his suprapubic wound had healed and his residual urine measured only 7 oz.

The radioactivity of the patient was investigated by Dr. J. S. Fulton and Dr. W. Kulke of the Liverpool Radium Institute who reported as follows:

The attempts to measure the radioactivity of this patient's returned Thorotrast were divided into two:

(1) Alpha particle measurement.

(2) Gamma ray detection.

(1) The fifth product in the disintegration series of thorium is thoron—a radioactive gas which emits alpha particles detectable in the expired air. The measurements were performed at Harwell by Dr. J. Sharpe using the method and apparatus described by Ward and Jensen (1951). 425 atoms of thoron were detected in each litre of expired air. From this figure and the assumption quoted in the paper that 1% of the thoron is expired, the amount of thorium was calculated to be 0·68 gramme which gives a figure of 5·16 c.c. of Thorotrast within the patient.

(2) The gamma rays arising during the disintegration of the thorium series come from mesothorium 11, 0·06 to 0·9 Mev, radiothorium 0·8 Mev and thorium C″ 2·6 Mev. Many attempts to measure these rays have been made. Geiger Müller counters G.M.4 and G.M.10 have been tried, as well as a scintillation counter designed by Mr. Herbert, having an improved background and sensitivity. 100 minute counts were recorded on occasions but no readings of statistical significance were obtained.

More recently Dr. T. A. Chalmers suggested measuring the volume of Thorotrast showing in the radiographs by comparing the density with known amounts of Thorotrast included in the radiograph. Continuous and step wedges of Thorotrast were used but interpretation was not successful, and the method was replaced by one in which the radio-opaque areas were accurately traced on to millimetre-squared paper and the area and volume of each opacity obtained.

This gave a value of 1·5 to 2 c.c. of Thorotrast in the skull and 1·0 to 1·5 c.c. in the cauda equina region. These are minimal values and indicate at least 3 c.c. of Thorotrast within the body. Work is at present in progress to determine the minimum amount of Thorotrast which in a body phantom could be detected by its gamma-ray emission.

Radiographs of the patient's liver and spleen showed no increase in density suggestive of Thorotrast deposit in these regions, and no radioactivity was detected over these organs.

It would appear from these measurements that practically all the original 5 c.c. of Thorotrast is still within the patient.

Few references occur in the literature to similar attempts at measurement of radioactivity of Thorotrast. Taft (1937) demonstrated the gamma radiation from the liver area of a patient who had had 75 c.c. of Thorotrast injected intravenously. He estimated that this was equivalent to the radiation from 1·37 μg. of radium. At autopsy he showed 50% of the original dose to be in the liver and 12% in the spleen.

Kantzmann, Gros and Meyer (1950) describe measurements on 2 cases of perivascular injections where counts ranging from 4 to $9 \times 10^{-10}$ r/sec. were obtained, over liver, spleen and injection sites.

Struppler (1952) describes a thorotrastoma developing after arteriography with 30 c.c. of Thorotrast into both carotid arteries. From his measurements twenty-three years after the injections he considers that several thousand roentgen may be delivered by alpha irradiation of the immediate surroundings. From physical principles Dr. Chalmers has calculated that 1 gramme of thorium distributed through 100 grammes of wet tissue for twenty years would deliver approximately 1,000 roentgens to that tissue.

I have not been able to find an article dealing with the measurement of Thorotrast in the cerebral ventricles or spinal cord.

Ward and Jensen (1952) describe "an apparatus designed for large measurements on patients contaminated by thorium".

Their results will probably be the leading paper at one of the General Meetings at the 1953 International Congress of Radiology at Copenhagen (1952, *Brit. J. Radiol.*, **25,** 588) devoted to "Contrast media in diagnosis and risks associated therewith".

## Discussion

The fate of Thorotrast introduced into the subarachnoid space and the histological changes produced were recorded early by Radovici and Meller (1932) and Wustmann (1933). These authors showed that the substance outlined the various parts of the brain and followed the prolongations of the sub-arachnoid space; owing to its high specific gravity the Thorotrast had a tendency to collect in the

more dependent situations. Immediately after the drug was injected a meningeal reaction was produced, macrophages were mobilized to ingest the dye resulting in increase in thickness of the pia mater. Excretion of the drug from the subarachnoid space was insignificant and it was found that it remained both there and within the cerebral ventricles permanently.

Alexander, Jung and Lyman (1934) described similar changes when Thorotrast was injected into the lateral ventricle of the dog and also noted histological changes when the drug was injected into the brain substance. Freeman, Schoenfield and Moore (1936) described the histological changes found in patients who had died at varying intervals after Thorotrast ventriculography and were of the opinion that while an inflammatory reaction was produced in the ventricles and subarachnoid space, this was transient so long as there was no obstruction to the flow of cerebrospinal fluid. They felt that it was safe to inject the drug into the cerebral ventricles. The transient nature of the reaction has not been confirmed by other workers either in the experimental animal or in man. Benes (1939) described the histological changes found in a 5-year-old girl who died twenty-seven days after Thorotrast ventriculography; despite the fact that there was no obstruction to the flow of cerebrospinal fluid a large amount of Thorotrast was present in macrophages in the ventricles and in the subarachnoid space and extensive desquamation of the ependyma of the ventricles had taken place.

In a comprehensive review of the use of Thorotrast for ventriculography and encephalography Reeves and Stuck (1938) stressed the serious inflammatory reaction which might be produced. Working with dogs, cats and monkeys they showed that hydrocephalus of a marked degree could be produced within as short a period as three months. They concluded:

> "Because of the indefinite retention of Thorotrast in the subarachnoid spaces, affording the possible development of cicatrices, its presence in the optic and other cranial nerves, as well as its location in the internal ear, with obvious opportunity for radioactive effect here and throughout the subarachnoid spaces, and in view of its partial obstruction to cerebrospinal fluid absorption with resultant hydrocephalus, we feel that the material should be unequivocally condemned for encephalography or ventriculography."

These authors thus predicted, as a result of the animal experiments, the possible occurrence of hydrocephalus and of damage to the cranial or spinal nerves. No other case of chronic damage to the nervous system appears to have been reported in the literature, presumably owing to the small number of cases in which Thorotrast was injected into the cerebral ventricles and the fatal nature of the conditions in which it was used.

The above changes in both animals and man occurred within a short period after the injection of the drug and hence could very well be explained as a result of the irritant nature of the substance injected. In the present instance, however, the radio-active material has remained within the skull and the spinal theca for a period of thirteen years and hence certain of the changes may very well be due to radioactivity. That changes in the nervous system can occur as a result of radioactivity is now well established.

A series of 10 cases of radiation myelitis following irradiation of malignant conditions about the neck was reported by Boden (1948) and cases of hydrocephalus following irradiation of the scalp for fungoid infections have been described by Schaltenbrand (1935) and Lorey and Schaltenbrand (1932). I have seen one similar case following irradiation of the orbit for a malignant tumour at the age of 9 years. In all 3 of these cases the brain was irradiated in childhood, hence it is uncertain if the same result would be produced by irradiation of the adult.

The cauda equina lesion in the present case could be explained satisfactorily on the basis of an arachnoiditis due to chemical irritation but again radioactivity must be taken into account as a possible contributory factor. It is, of course, a matter of dispute whether radiation myelitis is due to a direct action on the nervous tissue or whether it is secondary to changes in the blood vessels. The radioactivity of Thorotrast introduced into the body in small quantities is due largely to alpha particles, while the destructive effect of deep X-ray therapy is due to gamma radiations, the alpha and beta particles being filtered off by the superficial tissues. The alpha particles in particular are short in range and filtered off by a very thin layer of tissue, hence even when applied both to the inner and outer surfaces of the cerebral hemispheres Thorotrast would be unlikely to produce more than a very minor degree of brain atrophy as a direct action on the brain tissue. If the blood vessels were damaged, however, much more extensive changes could be produced. At the lower end of the spinal theca the comparatively thin roots of the cauda equina could sustain serious damage as a direct result of alpha particles.

There is a further possibility which must be considered in the present case and that is that the patient may ultimately develop malignant disease somewhere within the nervous system. The occurrence of malignant disease arising as a result of Thorotrast introduced into the systemic circulation is now well established and has been extensively investigated, but it is curious that this possibility has never been considered after the injection of the substance into the subarachnoid space. There is as yet no evidence of the presence of malignant disease in the present instance but it is my intention to keep this case under prolonged observation with this in view.

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**Brain-Stem Angioma Confirmed by Arteriography. Relapsing Symptoms and Signs Strongly Suggestive of Disseminated Sclerosis.**—RAYMOND HIERONS, M.B., M.R.C.P. (for DENIS BRINTON, D.M., F.R.C.P.).

Mrs. J. B., aged 26.

*Past history and family history.*—Not relevant.

She left school two standards below the top. She is left-handed, the other members of her family being right-handed.

For the last four years she has complained of very severe facial pain which has the typical qualities and precipitating factors of trigeminal neuralgia except for the tendency to a great deal of spontaneous pain and with an unusual seasonal incidence of pain, only from March to October. The pain is confined to the 2nd and 3rd divisions. In three seasons it has occurred on the right side and only once, in 1950, on the left.

Soon after the onset this year she developed temporary numbness of the palate and tongue on one side and later blurring of vision, possibly of the left eye for about two weeks. Three months prior to admission she noticed slight weakness of the right arm and leg for about a month. In earlier life she had been liable to a beating noise in the head but has not noticed this for some years. For the past three years she has occasionally been unsteady in walking.

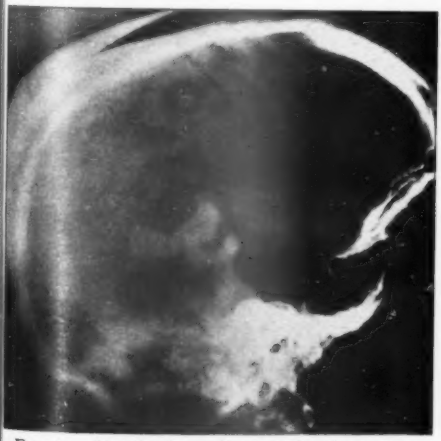

FIG. 1.—Vertebral arteriogram showing a large posterior cerebral artery and the mass of vessels outlined by dye filling the posterior fossa.

FIG. 2.—A.P. of vertebral arteriogram showing angiomatous vessels to be in the mid-line draining into the straight sinus.

The diagnosis of disseminated sclerosis had been made in the neurological Out-patients of two London Teaching Hospitals.

*The positive findings* included: slightly below average intelligence.

Speech: variable slurred dysarthria.

Spontaneous nystagmus of rotatory quality to the left persisting on the upward and downward position of gaze.

The face is slightly smaller on the right and occasional clonic spasm present in the right cheek and over the lower jaw.

Minimal cerebellar signs present in the right arm and leg.

In the left arm and leg slightly increased tone, weakness, increased reflexes and equivocal plantar response.

No impairment to any form of sensation.

An extremely loud bruit audible over the right mastoid process which is only faintly heard over the right eye.

Hirsuties of the chin.

A right carotid arteriogram (Dr. G. Thompson) showed most of the dye in a large right posterior cerebral artery supplying a large posterior fossa angioma. A vertebral arteriogram showed rather clearer filling of the angiomatous mass, the posterior fossa being filled with vascular ramifications (Fig. 1). In the A.P. view (Fig. 2) the main vessel is seen to lie in the mid-line and early drainage into the straight sinus is seen.

**Dr. Wilfred Harris** said that an angioma compressing the trigeminal nerve slightly at the base might cause pain somewhat resembling tic douloureux. Alcohol injection into the gasserian ganglion might relieve the pain for a time although peripheral to the site of irritation, just as he had seen injection of the infra-orbital nerve relieve maxillary neuralgia.

**Dr. J. Purdon Martin** said that he had encountered 2 cases of angioma of the brain-stem, which had been confirmed post mortem, and in both of them the course, because of its exacerbations and remissions, and also because of the nature of the signs, was very similar to that of disseminated sclerosis. He showed lantern slides illustrating the pathological findings in these 2 cases.

**Syndrome of Subacute Combined Degeneration Without Anæmia or Achlorhydria, Responding to Vitamin $B_{12}$.**—DENIS WILLIAMS, M.D., F.R.C.P.

A retired chauffeur, aged 68, had increasing numbness of both feet with cramp in the calves three years ago; sensation was reduced in the soles of both feet, and a numb cold feeling with "pins and needles" developed in the lower legs. Ataxia began and progressed. The condition slowly advanced and about a year ago similar symptoms appeared in both hands and advanced up the forearms.

Vision normal. Sphincters normal. No weight loss. Tongue sore for some months. Bilateral mild increasing deafness.

Mild indigestion for several years. Appetite and diet were satisfactory. He takes half a pint of stout a day. No family history of neurological diseases.

Patient was thin, pale; hair white and scanty. Tongue atrophic and dusky in colour. There was some arteriosclerosis. B.P. 150/80. There were no evidences of general medical disease.

*C.N.S.:* Cranial nerves were normal.

*Motor:* All muscles were small and the intrinsic muscles of the hands seemed wasted. There was tenderness of both calves. There was generalized reduction of muscle tone and mild inco-ordination of all limbs with ataxia and mild Rombergism. Moderate weakness was found in all peripheral muscles. Tendon reflexes were absent throughout, abdominal reflexes present, both plantar responses persistently extensor.

*Sensation:* There was hyperalgesia of the soles of both feet, loss of vibration sense in the toes with impairment in ankles and shins. Gross reduction of joint sense in the toes, reduction in light touch and pin-prick below the knees and slight subjective reduction of both in the fingers.

*Investigations.*—Blood count: R.B.C. 4·5 million per c.mm.; Hb 88% (13·0 g.); C.I. 1. Packed cell volume 40%. Mean corpuscular volume 89 cu.μ. Mean corpuscular hæmoglobin 29 μμg. Mean corpuscular hæmoglobin concentration 32%. Halo 7·7 μ. W.B.C. 11,600 per c.mm. Polys. 85, lymphos. 9, basos. 3, monos. 3%.

*Marrow puncture* (Dr. J. N. M. Chalmers, St. George's Hospital)*:* Normal differential count.

*Gastric analysis:* Free acid present after histamine test meal. Glucose tolerance test normal. Pyruvate test normal. C.S.F. normal (protein 50 mg.%). Urine—no porphyrins. Wassermann reaction negative in blood and C.S.F.

*E.S.R.:* 13 mm. in one hour. 27 mm. in two hours (Wintrobe).

*Radiology:* Chest: No evidence of tumour or lung disease. Barium meal and enema normal. Cervical spine: degenerative changes in the disc spaces: C5 and 6, 6 and 7. Treatment commenced 25.9.52, vitamin $B_{12}$ 100 micrograms twice weekly I.M.

*Progress.*—Re-examined at St. George's Hospital a month later. Pronounced subjective improvement in sensation of limbs, a reduction of paræsthesia, ataxia less marked, ability to walk improved. On examination, ataxia and Rombergism evidently better. Both plantar responses were now flexor.

**Professor F. J. Nattrass** felt that this syndrome could not be due to true subacute combined degeneration of the cord, though there were evidences of combined tract lesions.

**?Post-encephalitic Amyotrophy.**—K. W. G. HEATHFIELD, M.D., M.R.C.P. (for J. W. ALDREN TURNER, D.M., F.R.C.P.).

J. M., male, aged 28.

1944: Febrile illness whilst in Naples, in which he was somewhat drowsy. In hospital for some weeks.

1945: Discharged from Royal Navy with mitral stenosis. His mother noticed changed facial expression and slowness of his actions. He developed attacks in which the eyes rolled upwards and remained elevated for twenty minutes, about once or twice a week. Some dribbling from the left angle of the mouth. He developed some weakness of the arms, this gradually became more severe during the following years.

By 1949, weakness most marked in left arm and shoulder.

In the past year, he has been unable to dress or shave himself. Weakness has spread to affect hands as well as upper arms. No weakness of the legs, but some cramp of the calves at night.

*Past history.*—Aged 10, chorea and mitral stenosis.

*Family history.*—Irrelevant.

*On examination.*—Bovine expression with bilateral exophthalmos and lid retraction, and slow smile. Some blepharoclonus. Ocular movements full. Pupils react sluggishly to light, normally to convergence. Marked horizontal nystagmus to right and left. Bilateral lower facial weakness with fibrillation. Tongue wasted and fibrillating. Sternomastoids almost constantly fibrillating.

Arms: Gross wasting of both upper arms and shoulder girdles with fibrillation in deltoids, spinati and trapezii. Very gross weakness of both arms at shoulder and elbow. Extensors of fingers and wrists also very weak. Reflexes diminished in the arms. Some cog-wheel rigidity of the right wrist. Coarse rapid tremor of both hands when extended.

Legs: Normal power. No wasting. Tone normal. Almost continuous fibrillation in quadriceps and adductor muscles. Knee and ankle jerks brisk. Plantar responses flexor.

*Investigations.*—Hb 104%. W.B.C. 8,200 per c.mm. Differential normal. B.M.R. (10.6.52) +38%; (18.6.52) + 35%; (27.6.52) +29%. X-ray: slight enlargement of heart. No evidence of mitral stenosis. ECG, left ventricular hypertrophy. C.S.F., cells and protein normal. W.R. negative. Lange, no change.

Urinary creatine (13.6.52) nil; (30.6.52) 100 mg. in twenty-four hour specimen.

Serum protein-bound iodine, 8 mg. per 100 ml.

Radio-active iodine uptake, 43% in twenty-four hours.

Electromyogram, normal motor unit response in form but great reduction in number of units acting, also electrical confirmation of the clinical fasciculation.

*Treatment.*—In view of the raised B.M.R. he has been treated with thiouracil, but has not improved on this drug. The rigidity of the limbs has been helped with Artane 5 mg. b.d.

*Comment.*—This patient shows progressive weakness and wasting of the upper limbs with post-encephalitic Parkinsonism and mild thyrotoxicosis. The latter is a not uncommon sequel of encephalitis lethargica—Risak (1934) described 8 cases. Chronic anterior horn cell degeneration giving a clinical picture closely resembling progressive muscular atrophy was recorded in the epidemic years of encephalitis lethargica by several authors—e.g. Froment (1925), Wimmer (1928)—the subject is reviewed by Kinnier Wilson (1940). The electromyogram supports a neurogenic origin; thyrotoxic myopathy has been suggested but is unlikely in view of electromyogram finding and the failure to respond to thiouracil.

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**Dr. A. M. G. Campbell** said that he had at the moment under his care a similar case of a male patient of 28, with well-marked right-sided extra-pyramidal rigidity and wasting of the facial muscles and the sternomastoids. The sternomastoids were, as in Dr. Heathfield's case, constantly fibrillating. There was, however, no thyroid factor in his own case and no history of any illness in the past, apart from a febrile illness with rather vague symptoms at the age of 10.

He (Dr. Campbell) was convinced that the whole picture was explained by an attack of encephalitis and that the muscle wasting was part of a post-encephalitic amyotrophy.

**Intermittent Attacks of Confusion and Tremor Associated with Cirrhosis of Liver.**—T. GRAHAME WILSON, M.R.C.P.Ed. (for DOUGLAS MCALPINE, M.D., F.R.C.P.)

R. B., male, aged 39.

No family history of any nervous or mental disease.

1934: Malignant tertian malaria: no recurrence.

1944: Wounded in right thigh by phosphorus bullet.

May 1950: Acute attack of abdominal pain lasting a few hours.

September 1950: Recurrence of abdominal pain: admitted to the Middlesex Hospital. Liver and spleen found to be enlarged, without clinical jaundice, although excess urobilinogen in the urine. Biopsy of the liver showed coarse nodular cirrhosis. Patient discharged on a high protein-low fat diet with methionine.

October 1951: He became increasingly tired and developed slight intermittent tremor of the hands.

August 1952: Had the first of three attacks of confusion and tremor. They commenced with generalized malaise, alternating feeling of hot and cold with increasing tremor of the hands and face. Thereafter he became confused and was incontinent of urine. Temperature 96° F.

Attacks last two to three days, during which time he tended to sleep both day and night.

Between these episodes he was mentally normal, although retaining a fixity of expression, slight tremor of the hands on movement and mild slurring dysarthria.

*On examination.*—A sallow complexioned, ill-looking man, with a lack of facial expression. Spider nævi present over the chest and arms with patchy brownish pigmentation of the lips. Liver dullness was decreased: no dilated veins. Mild slurring dysarthria. Pupils and fundi normal: no K.F. ring. Coarse irregular tremor of the protruded tongue and lower jaw: no palatal myoclonus. Coarse irregular tremor of flexion-extension type at the fingers and wrists on sustained posture, appearing a few moments after the act is initiated, and becoming worse on attempting any co-ordinated movement.

All tendon reflexes brisk L > R with bilateral flexor plantar responses. No defect of muscular power or alteration of tone.

*Investigations.*—Liver functions markedly impaired. Copper excretion normal. Amino-acid excretion once above normal range, but no marked abnormality of chromatographic pattern seen (Dr. J. N. Cumings).

C.S.F. 1 lymphocyte, total protein 20 mg.%. Lange, no precipitation. W.R. negative. Air encephalogram was normal.

*Comment.*—It is postulated that the recurrent attacks of confusion and tremor are the result of an intermittent biochemical upset, possibly of essential amino-acids, dependent upon the degree of hepatic damage present. The nature of this upset is at present imperfectly understood.

POSTSCRIPT (March 1953).—During November and December 1952 the patient continued to have intermittent attacks of tremor and confusion similar to those already described.

Towards the end of December he developed œdema of the lower extremities and abdominal distension with some ascites. From this time until his death there were no further episodes of confusion, although he was persistently slightly drowsy. The abnormal neurological signs previously noted had disappeared. His condition slowly deteriorated and it became clear that he was entering the terminal stage of hepatic failure. He died in coma on February 4, 1953.

Post-mortem examination showed a liver which was shrunken to half the normal size, and presented the macroscopic picture of a coarse nodular cirrhosis. The spleen was enlarged, soft and congested. There were no naked-eye changes in the central nervous system which could be related to the intermittent episodes observed or to the abnormal neurological signs discovered.—T. G. W.

**Dr. Michael Jefferson** thought the occurrence of more or less transient episodes of disturbance of consciousness, ranging from slight confusion to deep coma, was a fairly well-recognized complication of hepatic cirrhosis, and seemed to be a different thing from terminal cholæmic stupor. Whitfield, A. G. W., and Arnott, W. M. (1951, *Brit. med. J.*, ii, 1054) described 3 cases showing this feature, 1 of whom he had the chance to see. None presented abnormal neurological signs, either apart from or during their attacks, and in 2, who later came to autopsy, there were no naked eye or microscopic lesions in the central nervous system which could be related to them. The mechanism of production of disordered consciousness in these cases was extremely obscure, but it must be presumed to depend upon a temporary and reversible biochemical upset.

**Involuntary Movements.**—J. V. GORDON, M.D., M.R.C.P., M.R.A.C.P. (for E. A. CARMICHAEL, C.B.E., F.R.C.P.).

Girl, aged 10 years. Two brothers, aged 11 and 26, alive and well. No family history of any nervous disease.

Birth was normal but mild jaundice was noted for the first three days and rectal hæmorrhage occurred on the third and seventh days. There was a little difficulty in swallowing at first and the child's limbs appeared stiff causing some difficulty in dressing her. She has never been able to sit up unsupported or stand by herself.

Abnormal movements of the legs and arms were first noticed at the age of 2. Initially of slight

severity, they have become more marked as the child has become older. The legs are more affected than the arms and the right arm more than the left. Isolated words were first said at the age of 4 and her speech has gradually improved but is hesitant and jerky.

*On examination* the child appeared quite cheerful and of average intelligence. Her speech was slow and dysarthric. Apart from an exaggerated smile no abnormality of the cranial nerves was found.

Except for brief moments there were continuous involuntary movements of the legs and arms with the legs being much more affected than the arms. The movements were violent and rapid, occurring at all joints especially from the proximal ones. They were asynergic and ballismic in nature being intensified by voluntary effort or emotional factors. Tone was normal and no actual weakness of her limbs could be established.

The plantar responses were flexor. Sensation was normal.

It is suggested that this is a case of ballismus probably due to lesions of the subthalamic nuclei. The underlying pathology must remain obscure. The history of infantile jaundice suggested kernicterus but investigation of the blood groups of mother, father and child revealed no incompatibility.

**Dr. J. Purdon Martin** said that he would agree with the description of bilateral hemi-ballismus. He was horrified at the suggestion of cortical excision which had been made in discussion. He referred to the recent experimental work of Mettler and his co-workers who had shown that in monkeys hemichorea, consequent upon a lesion of the corpus luysi, could be abolished by destruction of the medial portion of the globus pallidus, or by division of the ansa lenticularis.

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**Congenital Athetosis of the Left Hand Treated by Topectomy.**—A. C. SCHWIEGER, M.D., M.R.C.P., M.R.A.C.P. (for MACDONALD CRITCHLEY, M.D., F.R.C.P.).

W. McA., a man aged 28, complained of involuntary writhing movements affecting the left hand and twitching of the left side of the face, since birth.

History of damage to the head during a difficult labour.

The pattern of the movements had not changed over the years but had increased in severity under conditions of stress. At these times he was rendered dysarthric by twitching at the left corner of the mouth.

Athetoid movements were present affecting chiefly the left hand and fingers, involuntary movements taking place at the shoulder and elbow only under conditions of stress. There was slight weakness in wrist and finger movements. Myoclonic contractions occurred at the left nasolabial fold resulting in dysarthria. On voluntary movement there was slight weakness at the left corner of the mouth with over-reaction on involuntary movements. An isolated involuntary movement involving the left foot was occasionally seen. His gait was slightly hemiplegic. The tendon reflexes and superficial abdominal reflexes were brisk and equal and the plantar reflexes flexor. There was no sensory loss.

Investigations including air encephalography did not reveal any significant abnormality.

Dr. S. Allison, under whose care the patient had been, raised the question of surgical intervention, for it was considered that local excision of the hand and forearm areas would be a reasonable and effective exchange for his present state.

At operation (Mr. Wylie McKissock) the hand and forearm areas of the motor cortex were mapped out by stimulation (Dr. J. A. V. Bates) and excised by means of diathermy and suction, all grey matter being removed from the posterior part of the convolution down to the bottom of the Rolandic fissure. The depth of the excision here was nearly 2 cm. but anteriorly the convolution was shallower and the excision was 1 cm. The length of cortex removed measured 3 cm.

After operation he developed a flaccid paralysis and profound sensory loss affecting the left upper limb, moderate weakness of the lower limb and dysarthria. Within a few days well-marked spasticity developed in the left upper limb and tonic reflexes could be elicited. The sensory loss gradually disappeared over the course of a month and he began to show a return of voluntary movement at the shoulder and elbow but none at the wrist and fingers. The dysarthria and weakness of the left lower limb decreased and finally disappeared. His tendon reflexes were brisker on the left-hand side and the left plantar reflex was extensor.

Six weeks after operation power at the left shoulder and elbow had considerably improved, but there was no sign of return of any involuntary movements.

The patient expressed himself as being "very content" with the result of operation and was discharged on phenobarbitone prophylactically.

**? Sensory Radicular Neuropathy.**—J. HAMILTON PATERSON, M.D.

The patient is a single man, aged 30, complaining of callosities of the feet and severe deafness.

*History.*—About four years ago he developed a troublesome callosity on the sole of the right foot which was somewhat painful at first. When excised a year ago it was found to have penetrated to the

underlying bones; secondary osteitis of the first metatarsal ensued, the wound healing slowly. Three months later a dorsal abscess in this situation was drained, but he subsequently developed cellulitis of the foot. This has now subsided. Six months ago he was found to have a perforating ulcer of the left big toe from which a bony sequestrum was later removed. His deafness dates back for some twelve years; it was gradual in onset but it has been severe for at least three years.

*Previous medical history.*—Not relevant.

*Family history.*—2 of 8 siblings are deaf from obscure causes, his mother and her sister have also been deaf for some time. No history of perforating ulcers obtained.

*Findings on examination.*—A well-nourished but mentally retarded man who has severe bilateral deafness. Callosities with perforating ulcers on the sole of the right foot and under the left big toe. Peripheral vascular system normal.

Cranial nerves normal (apart from deafness).

Motor system normal save for slight ataxia of the lower limbs.

Reflexes: all tendon reflexes absent apart from both triceps jerks and the left knee-jerk which are just obtainable.

Sensation normal in upper limbs and trunk; definite hypalgesia and hypæsthesia over toes and feet with gradually fading area of slight impairment of pain appreciation up to knees. Position sense definitely impaired in toes; vibration sense much reduced at toes and malleoli. Stance unsteady with eyes closed. Gait somewhat ataxic and clumsy.

*Investigations.*—X-rays of feet show on the right, destruction of the distal ends of the 1st, 2nd and 3rd metatarsals and the proximal end of the 1st phalanx of the big toe; and, on the left, destruction of the interphalangeal joint of the left hallux.

Lumbar puncture: C.S.F. normal.

Blood and C.S.F. Wassermann reactions negative.

**Dr. A. M. G. Campbell** asked if this was not a case of familial sensory radicular neuropathy in which deafness had been described as part of the syndrome. In a family he had investigated both father and son had shown gross destruction of the bones in the feet, particularly of the 1st, 2nd and 3rd metatarsal.

**Dr. Paterson** agreed that this was probably so, though sporadic cases of a similar order had also been recorded.

**Obliteration of the Right Internal Carotid Artery with Subarachnoid Hæmorrhage.**—P. K. ROBINSON, M.B., M.R.C.P. (for Sir CHARLES SYMONDS, K.B.E., C.B., M.D.).

Mrs. T. R., aged 34. No significant family history. History of migraine since the age of 14, with headaches, vomiting and transient weakness of left hand.

On 13.9.52: Sudden onset of left hemiplegia with right frontal headache, but without loss of consciousness. Low-grade fever on sixth day. 17.9.52: Admitted to Plaistow Hospital. Conscious but confused. Complete left hemiplegia with sensory loss to all modalities, and left homonymous hemianopia. Pupils normal, but right-sided ptosis. Neck stiffness. C.S.F. under increased pressure; blood-stained with yellowish supernatant fluid. R.B.C. 300 per c.mm. W.B.C. 13 per c.mm.

19.9.52: Transferred to National Hospital. Stuporous and confused. Complete left hemiplegia with sensory loss and hemianopia; loss of left corneal reflex. Right pupil dilated with faint light reaction; left pupil small and fixed. Bilateral VI nerve palsies and limitation of upward gaze. No deep reflexes; both plantars extensor. B.P. 115/80. Right carotid pulse less prominent than left. No skull bruit. C.S.F. (19.9.52) pressure 300 mm. +. R.B.C. 400 per c.mm. W.B.C. 75 per c.mm. Protein 60 mg.%.

*Arteriography* (Dr. G. Thompson).—Narrow right internal carotid artery. This appeared to be obstructed at the back of the carotid siphon. Right posterior cerebral artery filled, but right anterior and middle cerebral arteries were only filled from left internal carotid artery which was large. Possibility of a small angioma in the region of right posterior cerebral artery.

*Progress.*—Fourteen days: Ocular palsies almost cleared. Seventeen days: Commencing recovery of motor and sensory functions in left arm and leg. Now has a left lower quadrantic field defect, left hemiparesis with more sensory deficit than motor. Left pupil larger than right but ocular movements full. Left corneal reflex remains impaired. No skull bruit, but audible bruit over upper part of left carotid artery.

# Section of Odontology

President—E. Wilfred Fish, C.B.E., M.D., F.D.S. R.C.S.

[*November* 24, 1952]

## Streptococci of the Mouth and Their Relationship to Subacute Bacterial Endocarditis

By E. Desmond Farmer, B.A., M.D.S., F.D.S. R.C.S.

*Lecturer in Parodontal Diseases, School of Dental Surgery, University of Liverpool*

Summary.—Streptococci isolated from the mouths of 25 apparently normal individuals were examined serologically and 37% were found to be members of Lancefield groups. Groups H and K and, to a lesser degree, Groups F and O were most commonly represented. Members of more than one group were frequently found in the same mouth. While many of the strains that were not members of Lancefield groups were serologically heterologous, 24 strains appeared to share some antigens with the Group H streptococci, and 18 other strains were tentatively classified into three small groups. The cultural and biochemical characteristics of all strains were investigated and the similarity between some strains of *Str. sanguis* and the Group H streptococci is stressed.

Four cases of subacute bacterial endocarditis were investigated in an attempt to find serologically identical organisms in the blood and in the mouth. Group H streptococci were isolated from the blood of two of the patients and in one of these cases a Group H strain was also isolated from the mouth. The two Group H strains isolated from the same patient were found to belong to different serological sub-groups of Group H, but the strains isolated from the blood of the patients with subacute bacterial endocarditis were found to be serologically similar to the majority of those isolated from the mouths of normal patients.

The purpose of this paper is to consider the streptococci found in the mouths of normal patients; to compare their characteristics with the streptococci reported as having been isolated from the blood of patients with subacute bacterial endocarditis; and finally to discuss the role of the mouth as a possible focus of infection in the ætiology of subacute bacterial endocarditis.

An investigation concerned with the identification of streptococci is complicated by the fact that no single criterion has been found on which a classification can be based. It is not intended to discuss in detail all the work which has been done in this field, but merely to summarize the many attempts that have been made to classify streptococci. The characteristics that have been considered are briefly these; the length of chain formed in fluid medium, the type of hæmolysis produced on blood agar (Schottmüller, 1903; Smith and Brown, 1915; Brown, 1919), and the results of cultural and biochemical tests (Andrews and Horder, 1906; Holman, 1916; Sherman, 1937) and of serological tests. The latter include complement-fixation (Kinsella and Swift, 1917; Howell, 1918; Hitchcock, 1925), agglutination (Griffith, 1926, 1934) and precipitation (Lancefield, 1933, 1934, 1938, 1941).

Using the type of hæmolysis produced on blood agar, it is found that many of the non-pathogenic streptococci belong to the α-hæmolytic or viridans group, while those isolated from infections in man are usually β-hæmolytic. However, hæmolysis cannot be regarded as a certain guide to the pathogenicity of the streptococci as β-hæmolytic strains are frequently isolated from normal mouths

and throats (Lancefield, 1941; Lancefield and Hare, 1935; Long and Bliss, 1934; Bliss, 1937; Hare, 1935), while occasionally viridans strains are found to be the cause of diseases in man (Coburn and Pauli, 1941; Colebrook *et al.*, 1942).

In 1933 Lancefield found that many of the β-hæmolytic streptococci could be classified by using the precipitation technique. This simple serological technique, based on the presence in the organisms of an acid-soluble group-specific substance usually a polysaccharide, is reliable, particularly for those streptococci pathogenic for man and animals. The streptococci classified by this method have been divided into 13 groups, there being a close relationship between the source and pathogenicity of the strain and the presence of the group-specific polysaccharide.

The relationship between the source of the streptococci and the presence of the group-specific substance was clearly illustrated by Lancefield (1941). It was shown that Group A streptococci are frequently pathogenic for man, Group B for cattle and Group C for horses, while members of Groups F, G, H and K are usually non-pathogenic and are often found in the normal human nasopharynx. In addition, streptococci designated Group O by Boissard and Wormald (1950) are also found in the normal human mouth and nasopharynx. Members of most of these groups have been divided into types. For example, the Group A streptococci have been divided by agglutination and precipitation into 32 or more types, the pathogenicity of the strain being directly related to the presence of certain type-antigens.

Although the Lancefield classification is primarily a classification of β-hæmolytic streptococci, some viridans strains have been identified within these groups, and attempts have been made to classify other green-producing strains by using this precipitation technique. Soloway (1942) examined 207 viridans streptococci isolated from the teeth and throats of normal patients and from the blood of patients with subacute bacterial endocarditis. She considered that 136 of these strains could be divided by the precipitation technique into 14 groups, the majority of the strains being included within 4 groups. In 1949 Selbie, Simon and Robinson, using a similar technique but with less specific sera, examined 209 strains isolated from the same sources as Soloway and divided 181 of them into 3 main groups and 2 subsidiary groups. Both these investigations showed that some of the streptococci isolated from normal mouths possessed certain antigenic characteristics in common with some of the streptococci from the blood of patients with subacute bacterial endocarditis.

There are many streptococci that cannot be identified satisfactorily by serological methods and among these are a large number of strains found in the mouth, which, at present, are identified by their cultural and biochemical reactions.

Sherman *et al.* (1943) considered that most of the streptococci in the mouth, not classified by serological methods, can be divided into those that produce large mucoid colonies when grown under aerobic conditions on 5% sucrose agar, and those which do not. Using the terminology introduced by Andrews and Horder (1906), Sherman labelled the first group *Str. salivarius*, and the second *Str. mitis*. It was found that out of 331 mouth strains, 184 could be classified as *Str. salivarius* and 147 as *Str. mitis*, the former being a relatively homogeneous group of organisms while those classified as *Str. mitis* formed a relatively heterogeneous group.

Other streptococci identified by cultural and biochemical methods, and reported as being isolated from the mouth, include *Str. equinus*, a non-lactose-fermenting organism (Andrews and Horder, 1906); *Streptococcus M.G.* isolated from the mouths and throats of several patients with primary atypical pneumonia (Mirick *et al.*, 1944); and *Str. mutans*, isolated by Clarke (1924) and described in detail by Maclean (1927) and thought to be associated with the ætiology of dental caries.

The formation of large mucoid colonies by *Str. salivarius* is regarded by many workers as a fairly reliable means of identification. Unfortunately, most of the other streptococci are notoriously unreliable in their biochemical and cultural behaviour, and, because of this, the serological method of classification was used as the basis of the investigation about to be described. The cultural and biochemical characteristics were also investigated, but only those of a limited number of strains will be discussed here.

## Procedure

Samples were taken from the saliva and gingival sulci of 25 apparently normal patients, the state of the oral hygiene and the depth of gingival sulci being noted. These samples were spread on to horse-blood agar plates and incubated for twenty-four hours under aerobic conditions. After this period, streptococcal colonies were picked off and spread on to fresh blood agar plates, the nature of the colony and type of hæmolysis being noted. From these pure cultures extracts were prepared and were tested against the grouping sera for all Lancefield groups, excluding Groups M and N.

## Results

194 strains of streptococci were examined and 71 or 37% were identified as members of Lancefield groups. Table I shows the groups most frequently represented.

Table I.—Number of Mouths from which were Isolated Members of Lancefield Groups

| Streptococci belonging to Lancefield groups | No. of subjects from which representatives of each group were isolated. Total No. of mouths = 25 |
|---|---|
| H | 12 |
| K | 12 |
| F | 7 |
| O | 7 |
| G | 2 |
| B, D and A | 1 each |

An approximate estimation showed that Group H streptococci were present in fairly large numbers in 7 mouths, while members of Group K were found as an almost pure culture in 1 mouth and were present in fairly large numbers in 5 other mouths. Members of the other Lancefield groups were found in relatively small numbers in each of the cases from which they were isolated, apart from one case where several Group F colonies were present. Members of more than one Lancefield group were often found in the same mouth. For example, in one mouth 4 groups were represented, while 2 or 3 groups were commonly encountered.

It was found that there was no apparent relationship between the presence of the members of any of the Lancefield groups and the state of the oral hygiene or the depth of the gingival sulci in the mouths from which the bacteria were isolated.

In an attempt to classify serologically the streptococci not classified as members of Lancefield groups, precipitating antisera were prepared in rabbits using 25 strains of streptococci, and the acid extracts of the 194 strains were tested against the 25 prepared sera.

Table II.—Classification of 194 Strains of Streptococci Isolated from the Mouths of 25 Normal Patients

| No. of strains | Classification |
|---|---|
| 71 | Members of Lancefield groups |
| 24 | Serologically related to Lancefield Group H |
| 18 | Divided into 3 groups consisting of 10, 6 and 2 strains |
| 1 | *Str. salivarius* |
| 80 | Serologically heterologous (possibly *Str. mitis*) |

The results of this part of the investigation are included in Table II. It can be seen that 24 strains appeared to be serologically related to Group H streptococci, but the actual nature of this antigenic relationship was not determined. These 24 strains possessed many of the cultural and biochemical characteristics of the Group H streptococci. 18 other strains were divided into 3 groups. The remaining 80 strains were serologically heterologous and might conveniently be classified as *Str. mitis*. One strain classified by its cultural and biochemical characteristics was identified as *Str. salivarius*.

The cultural and biochemical characteristics of all the isolated streptococci were investigated, using the methods reported elsewhere (Farmer, 1951). Table III shows the characteristics of the members of Groups H and K.

It can be seen that 3, or 14%, of the Group K strains formed large mucoid colonies when grown aerobically on agar containing 5% sucrose—a factor considered by Sherman *et al.* (1943) to be characteristic of *Str. salivarius*. These 3 strains also possessed other characteristics of *Str. salivarius*, such as the ability to split æsculin, to ferment raffinose and inulin, rapidly to clot milk and to produce a low pH in 1% glucose broth. Similar findings among the Group K streptococci have been reported by Hehre and Neill (1946).

Although the members of Lancefield Groups H and K possess some similar characteristics, they differ particularly in their reaction with the carbohydrates raffinose and inulin; in the type of colonies produced after anaerobic incubation on 5% sucrose agar; in the formation of a serologically detectable dextran in sucrose broth, and the ability to grow on blood agar in the presence of bile.

TABLE III.—CULTURAL AND BIOCHEMICAL CHARACTERISTICS OF 22 MEMBERS OF LANCEFIELD GROUP K AND 28 MEMBERS OF LANCEFIELD GROUP H STREPTOCOCCI

| Cultural and biochemical test | Percentage number of strains showing the designated characteristic | |
|---|---|---|
| | Lancefield Group H (28 strains) | Lancefield Group K (22 strains) |
| Hæmolysis on horse-blood agar | | |
| Alpha and alpha-prime | 77 | 66 |
| Beta | 23 | 14 |
| Gamma | 0 | 20 |
| Fermentation of | | |
| Lactose | 94 | 100 |
| Glucose | 100 | 100 |
| Maltose | 100 | 100 |
| Saccharose | 100 | 100 |
| Sorbitol | 0 | 0 |
| Trehalose | 45 | 14 |
| Raffinose | 27 | 91 |
| Inulin | 65 | 14 |
| Dextrin | 16 | 38 |
| Æsculin | 32 | 14 |
| Salicin | 84 | 47 |
| Mannitol | 10 | 0 |
| Fermenting inulin but not raffinose | 43 | 0 |
| Hydrolysis of arginine | 90 | 43 |
| Production of mucoid colonies on sucrose agar after | | |
| Aerobic incubation | 0 | 14 |
| Anaerobic incubation | 48 | 0 |
| Visible gel formation in sucrose broth | 22 | 0 |
| Dextran formation in sucrose broth | 97 | 0 |
| Growth on blood agar in the presence of | | |
| 10% ox bile | 97 | 38 |
| 40% ox bile | 48 | 10 |
| Acid and clot in litmus milk | 78 | 33 |
| Reduction of 0·1% methylene blue in milk | 53 | 4 |
| Final pH in 1% glucose broth | 4·48 | 4·4 |
| Average range | 4·14–5·06 | 3·98–4·64 |

The Group H streptococci possess many of the cultural and biochemical characteristics attributed to a streptococcus first labelled *Streptococcus s.b.e.* by Loewe *et al.* (1946*a*), and later called *Str. sanguis*. Such characteristics include the hydrolysis of arginine, the fermentation of inulin while failing to ferment raffinose, the tolerance of 40% bile, and the ability to synthesize a detectable dextran from 5% sucrose broth. Loewe and his co-workers identified 41 strains of this streptococcus among the 106 strains isolated from the blood of patients with subacute bacterial endocarditis.

Attempts have been made to isolate *Str. sanguis* from the mouths and throats of normal individuals. White and Niven (1946) examined 820 strains isolated from 49 normal throats, but were unable to find one strain similar to *Str. sanguis*. They came to the conclusion that if *Str. sanguis* were present in the normal mouth and throat then it must be in very small numbers. More recently Snyder and Johnston (1952) examined several hundred specimens of human saliva and again were unable to find a strain of *Str. sanguis* in the mouth.

It has been shown by Dodd (1949), Porterfield (1950), and Farmer (1951) that many strains of *Str. sanguis* must be regarded as Lancefield Group H streptococci. In view of this, and the findings reported in Table I, it is difficult to account for the failure of the above workers to find *Str. sanguis* in the mouths and throats of normal individuals. A possible explanation of this failure is that in each case selective media were used for first isolation. White and Niven (1946) used the production of

large colonies after anaerobic cultivation on 5% sucrose agar for the isolation of 680 strains and later used growth in the presence of 30% bile for a further 140 strains. Assuming that many strains of *Str. sanguis* are members of Group H, it can be seen in Table III that neither of these characteristics are very reliable guides. Snyder and Johnston, on the other hand, used penicillin in 5% sucrose agar in an attempt to inhibit the growth of *Str. salivarius* and allow the growth of the dextran-producing *Str. sanguis*. It is not easy to understand the rationale of this method as strains of *Str. sanguis* have been shown to be sensitive to penicillin both *in vivo* and *in vitro* (Loewe *et al.*, 1946*a*; Loewe *et al.*, 1946*b*; Porterfield, 1950).

TABLE IV.—STREPTOCOCCI ISOLATED FROM THE BLOOD OF PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS

| Name | Date | No. of Strains investigated | *Str. salivarius* | *Str. fæcalis* | *Str. zymogenes* | *Str. mitis* | *Str. mastitidis* | *Str. bovis* | *Str. sanguis* | Lancefield groups | Not Identified |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | D G H K | |
| Moran | 1938 | 20 | 12 | 3 | 2 | — | — | — | — | — — — — | 3 R-types |
| Soloway | 1942 | 100 | 82 | — | — | — | — | — | — | — 1 — — | 18 |
| Penistan | 1945 | 1 | — | — | — | — | — | — | — | — — — 1 | — |
| Wheeler and Foley | 1945 | 21 (7 post mortem) | — | — | — | — | — | — | — | 16 — — — | 5 |
| Loewe *et al.* | 1946 (*a*) | 106 | — | 5 | — | 39 | 4 | 11 | 41 | — 1 Not tested | 5 |
| Porterfield | 1950 | 29 | — | — | — | — | — | — | — | 4 — 6 — | 19 |

| | | | Viridans streptococci | Non-hæmolytic streptococci | Entero-cocci | Other streptococci | |
|---|---|---|---|---|---|---|---|
| Cates and Christie | 1951 | 408 | 354 | 31 | 2 | 2 | |

A review of some of the micro-organisms isolated from the blood of patients with subacute bacterial endocarditis, summarized in Table IV, shows that prior to 1943 the strains isolated were frequently labelled *Str. salivarius*, but after the more limited definition of this streptococcus was introduced by Sherman *et al.*, in 1943, its isolation has been but rarely recorded.

Wheeler and Foley (1945) considered that out of 21 strains isolated from anti- and post-mortem cases of subacute bacterial endocarditis 16 were members of Group D.

Loewe and his co-workers (1946*a*) considered that *Str. sanguis* was the causative organism in at least one third of the cases they examined, and it can be assumed that many of these strains were members of Group H. The strains of *Str. fæcalis* identified by these workers were possibly members of Group D.

Porterfield (1950) found 6 of 29 strains to be members of Group H and 4 probably members of Group D. He concluded from his results and those of other workers that Group H streptococci were frequently the causative organism of subacute bacterial endocarditis.

Cates and Christie (1951) report that of the 408 strains isolated in 14 centres in Great Britain, 87% were viridans streptococci, 8% or 31 were non-hæmolytic streptococci, while 2 strains were classified as enterococci. This report also includes the results of Selbie, Simon and Robinson (1949) and Porterfield (1950).

In view of the reports of the isolation of Group H streptococci from the blood of patients with subacute bacterial endocarditis, and the frequent isolation from the mouths of normal patients of strains belonging to this group, it was decided to examine the streptococci isolated from the blood, and those present in the mouths, of the limited available number of patients with subacute bacterial endocarditis, in order to find whether serologically identical strains could be isolated from both sources.

### Investigation of Patients with Subacute Bacterial Endocarditis

Four patients with positive blood cultures were examined. From the blood of one patient a Group D strain was isolated. This patient had been edentulous for many years and was unfortunately not available for further examination. Of the 3 remaining blood strains 1 was not a member of a Lancefield group while the other 2 were both members of Lancefield Group H.

Mouth and throat swabs were taken at the same time as the first blood sample and from 3 of the patients further swabs were taken at different stages during and after treatment, which consisted of 2 million units of parenteral penicillin daily. The swabs were spread on to blood agar and examined in the manner used in the earlier part of this investigation. Precipitating antisera were prepared in rabbits using the strains isolated from the blood of the patients. These sera were then tested against the acid extracts of the mouth-strains isolated from the respective patients.

Many colonies were examined and on some occasions as many as 43 strains from each mouth were tested serologically. In one of the cases where Group H streptococci were isolated from the blood a Group H strain was also isolated from the mouth, but the Group H mouth strain was not found until five weeks after treatment had started. It is perhaps of interest to note that in this case the onset of the symptoms of the general condition were thought to be associated with the recent extraction of an upper right canine.

Lancefield Group H streptococci belong to at least three different types or sub-groups (Farmer, 1951), and it was found that the two Group H strains isolated from the mouth and the blood of the same patient were members of different sub-groups. However, the 2 Group H blood strains isolated from the 2 patients with subacute bacterial endocarditis were members of the same sub-group as the strains most commonly found in the mouths of normal patients, while the Group H mouth strain isolated from one case of subacute bacterial endocarditis was found to belong to the same sub-group as the largest number of blood strains isolated by Loewe *et al.* (1946*b*) and examined by Washburn, White and Niven (1946). It is probable, therefore, that there is very little difference between the distribution of the members of the different sub-groups of Group H.

No significant differences were found between the cultural and biochemical characteristics of the Group H strains isolated from the different sources in the patients with subacute bacterial endocarditis or from the mouths of the normal individuals.

### Discussion

In this paper it has been shown that 37% of the streptococci present in the mouths of 25 apparently normal patients could be classified as members of Lancefield serological groups. It has also been shown that many of the streptococci reported as being isolated from the blood of patients with subacute bacterial endocarditis are culturally, biochemically and serologically similar to those found in the mouths of almost half of the normal patients investigated.

It is generally agreed that in order to establish the valvular lesion of subacute bacterial endocarditis bacteria enter the blood stream and become lodged on, or in, a heart valve previously rendered in some way susceptible to infection (Hadfield and Garrod, 1948; MacIlwaine, 1947).

It has been established by Okell and Elliott (1935) and many other workers (Burket and Burn, 1937; McEntegart and Porterfield, 1949; Robinson *et al.*, 1950), that bacteria enter the blood stream during the extraction of teeth in about 40% of cases, but in only about 10% of cases of subacute bacterial endocarditis has the onset of symptoms been associated with recent dental extractions (Robinson *et al.*, 1950; Cates and Christie, 1951). Cates and Christie report that out of 215 patients 10·7% had a history of tooth extraction within three months prior to the onset of symptoms, and 48% had signs of dental sepsis.

According to Cates and Christie (1951) the incidence of subacute bacterial endocarditis in the general population of England and Wales is under 1,000 cases per year. It is difficult to estimate the total number of patients undergoing dental extractions in one year and it is even more difficult to estimate the number with dental sepsis, but it is evident that these numbers must be very high indeed. There is a possibility, therefore, that the association between tooth extraction and the ætiology of subacute bacterial endocarditis is purely coincidence.

Many workers have reported a similarity between the organisms in the blood and the organisms present in the mouths of patients with subacute bacterial endocarditis, but this similarity is usually confined to the type of hæmolysis produced on blood agar, or to the results of certain cultural and biochemical tests. If the mouth were the original source of the strain causing the heart lesion, it would be expected that serologically identical strains could be found in both the blood and the mouth of the patient concerned. It may be that by using serological methods further work will reveal identical strains from both sources, but as yet no such reports have been noted.

There are several possible reasons why identical strains have not been isolated from both sources even if they were originally present in the mouth. For example, the offending organism may have been a casual visitor to the mouth; or, the large number of bacteria in the mouth may mask the strain being looked for; or, it may be that the high antibody titre in the patient's serum prevents the strain from growing in the mouth, while the bacteria that have become established in the heart lesion, where they are protected by the surrounding fibrin and tissue elements, are relatively unaffected; or it may even be that an insufficient number of cases have been investigated.

It has been observed that members of Lancefield Groups D and H are frequent causes of subacute bacterial endocarditis. Members of these groups usually have a high tolerance of bile and are often found in normal fæces. It may be, therefore, that the bacteria causing the heart lesion have an opportunity to enter the blood stream at places in the alimentary canal other than from the mouth.

In conclusion, it must be emphasized that although it has not been established that the mouth is a focus of infection in the ætiology of subacute bacterial endocarditis, the finding in the mouths of normal patients of bacteria that are serologically similar to those isolated from the blood of many cases of subacute bacterial endocarditis, suggests that precautions should be taken to protect the patient with a susceptible heart lesion from the possible consequences of a bacteriæmia during dental operations.

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**Mr. Arthur Bulleid:** It is admitted that the β-hæmolytic streptococci have received a most adequate and comprehensive classification by Lancefield and that this group stands apart from the other groups, but I would join issue when Mr. Farmer says that members of this group are fairly frequent in the mouth.

Personally I think that true β-hæmolytic streptococci are infrequent in the mouth proper though they are more often found in the throat. The green-producing streptococci and the heterogeneous indifferent γ groups are by far the commonest types found in the mouth proper.

I have often wondered if the oral streptococci are merely strain variations of a few well-defined types or whether many should be exalted to named varieties. If we accept the fact that *Str. salivarius*, *Str. mitis*, *Str. equinus*, *Str. bovis*, *Str. fæcalis*, *Str. lactis*, *Str. pneumoniæ*, and *Str. pyogenes* can definitely be identified we still find that there are exceptions to a watertight classification whatever criteria are employed.

The interrelationship between the named species which can be identified in the mouth from amongst the heterogeneous group may be an indication that the oral streptococci form a continuous series in which named species serve only as a series of reference points.

Neither colony formation, biochemical, or cultural behaviour are good methods of classification and serological methods seem by far the most satisfactory.

From his investigations into the mouth flora Morris (1952) found that the most common streptococcus in the mouth is a minute non-hæmolytic organism with a colony so small that it can easily be missed, and in his opinion it is more common than *Str. salivarius*. He also states that all strains of streptococci produce hydrogen peroxide as shown by the benzidine plate method.

Some oral streptococci undoubtedly possess certain antigenic characteristics in common with some of the streptococci which are isolated from cases of subacute bacterial endocarditis.

It is not essential that there must be dental extractions to engender a streptococcal bacteriæmia, as it has been proved that even mastication in a mouth with obvious dental sepsis may produce the same effect, although it is, of course, possible that the streptococci may not reach the heart.

Mr. Farmer has stressed one important factor in the production of a subacute bacterial endocarditis: that there must be a lesion of the heart valves which renders them susceptible to infection. As the number of patients with old rheumatic heart lesions cannot be vast and as the number of patients with dental sepsis undoubtedly is, the number which are likely to get an endocarditis from the streptococcal bacteriæmia must be small.

Green-producing streptococci have been isolated both from the mouth and the blood in cases of subacute bacterial endocarditis, yet, only in a few cases apparently, have the serological identical strains been isolated from the mouths and blood of the same patient. As Mr. Farmer states this may be due to the fact that the streptococci found in the blood cultures in cases of subacute bacterial endocarditis may have been only casual visitors to the mouth but I am rather of the opinion that the ingress of accidental parasites into the mouth from the outside is not so common as supposed.

The fact, however, that many of the streptococci found in the mouth are serologically identical with those isolated from the blood of cases of subacute bacterial endocarditis though not necessarily in the same patient does suggest that cauterization of the supporting structures of the teeth should be carried out when extraction of teeth is called for in cases of a known valvular heart lesion.

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# Section of Ophthalmology

President—Professor W. J. B. RIDDELL, M.D., F.R.F.P.S., F.R.S.Ed.

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## Ocular Actinomycosis

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INFECTION of the eye with actinomycotic organisms is an exceedingly rare condition and Cogan (1949) could find only three proven cases in the literature in which a branching filamentous organism was responsible for an intra-ocular infection. To these he added one case of his own in which the fungus was found in sections. Birge (1952) also could find only scanty references to such infections.

Amongst the reported cases of actinomycosis of the eye there is only one in which the organism was isolated (Verhoeff, 1925) and in this case the patient died later of actinomycosis of the liver; it seems probable, therefore, that the intra-ocular infection may have been due to a metastatic ophthalmitis.

In only one other condition have I been able to find a description of these organisms in association with an intra-ocular infection. This is a case described by Hardy and Wedding (1946) in which they were able to isolate an actinomyces from an atypical case of Vogt-Koyanagi syndrome. The patient died and the organism was recovered from the cerebrospinal fluid and the aqueous. The problem arises as to whether the actinomyces was the cause of the condition; which would appear unlikely unless the Vogt-Koyanagi syndrome has a multiple ætiology.

In the ocular adnexa the situation is very different in that infections with fungi are not uncommon and at least 42 species have been described in these areas, of which a number fall into the genus Actinomyces.

Actinomyces are now divided into three main groups, the aerobic species which are classified as the Nocardia, the anaerobic forms obtained from human and bovine infections and the Streptomyces. These organisms may be indistinguishable microscopically, and can be differentiated only by cultural methods.

Clinically, infection by the Nocardia is rare despite their widespread distribution; the most common being pulmonary infections although primary lesions of brain and kidney have been described. In the eye Nocardia have been described as a cause of suppuration in the lacrimal sac (a case in which the organism was carried in by a grain of corn); in lesions of the conjunctiva and in cases of keratitis (Bruce and Locatcher-Khorazo, 1942, and Benedict and Iverson, 1944). To these may be added a case of our own in which the organism was isolated from a chronically discharging Cutler's implant.

The most frequent of all the infections of the extra-ocular tissues with actinomycotic organisms are those in which the organism is found in the lacrimal canaliculus. The occurrence of lacrimal concretions was noted by Cesoni in 1670, and Von Graefe in 1854 gave a detailed clinical description of the condition, while Cohn (1875) showed they were due to the presence of a fungus, which on morphological grounds he named *Streptothrix foersteri*, some two years before Harz (1877) described the organism of bovine actinomycosis. The fungus was not cultured until some years later when it was realized that these organisms were not Streptothrices but Actinomyces; thus the name streptothrix should not be applied to these organisms since the terms had previously been used for an entirely different group of fungi.

In the appearance of this condition there are two points I would emphasize. The concretion is attached at only one point to the wall of the canaliculus, so that although there may be a blockage of flow of tears the lacrimal canaliculus may be patent to syringing. The second point is that actinomycotic infection may be associated with a condition in which the presenting symptom is a conjuntivitis rather than a blockage of the canaliculus. Of the cases I have seen one had had a conjunctivitis for four and a half years before the concretions were found.

I would like to describe the bacteriological features of the organisms in a series of 15 cases seen during the last six months from which we have isolated 11 strains of Actinomyces, but before doing so it is interesting to compare our series of cases with the usual clinical description. It is said to be a

disease of women between 40 and 50 years of age and to be rare in men—in fact the recorded cases are almost exclusively in women from 40–60 years of age; the present series of 15 is unusual in that it includes 3 males, the youngest of whom was 19 and in that the ages ranged from 17–60. This series is the largest reported number of strains studied bacteriologically, hitherto only two or three strains have been investigated by any one worker.

*Isolation.*—Concretions were expressed from the canaliculus by digital pressure against a sterile throat swab inserted into the conjunctival sac. This enabled the concretion to be expressed from the lacrimal punctum.

When the concretion was expressed it was removed from the punctum with sterile forceps, washed in normal saline, 95% alcohol and saline again. Finally it was emulsified in saline and part was used for making a smear and the remainder inoculated into Brewer's medium and on to blood and chocolate agar plates which were incubated aerobically.

Incubation was continued for seven days aerobically and if the plates remained sterile (which they normally did) the Brewer's medium was not considered to be sterile until twenty-eight days had elapsed.

From 11 of 15 cases in which this technique was used the organism was isolated when it was present in the smear, and in every case in which a concretion was present in the canaliculus it was possible to find branching filaments (Figs. 1 and 2).

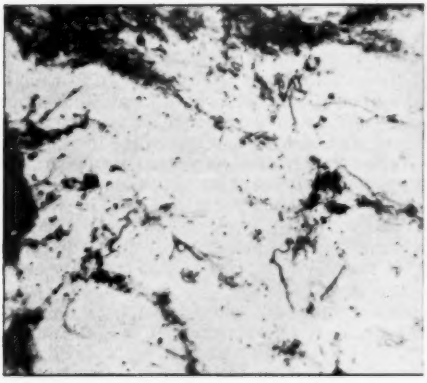


FIG. 1.—Smear from concretion showing filaments and small coccoid bodies. Gram stain × 1,200.

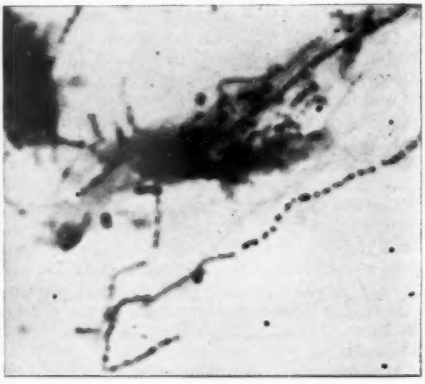


FIG. 2.—Filament from a concretion showing beaded appearance. × 1,200.

## CULTURAL CHARACTERS

All strains grew well in Brewer's medium on primary isolation but varied in the time at which growth appeared from seventy-two hours with strain IV, to fourteen days with strain VII.

Growth was usually maximal in the area immediately below the aerobic zone although scattered colonies appeared through the anaerobic area of the medium (Fig. 3A). A similar appearance was found with agar shake cultures sealed with paraffin. This appearance was found with most strains; however, three strains showed a slightly different appearance with a rather characteristic small colony from which a plume growth hung down (Fig. 3B) the plume consisting of pin-point satellite colonies; a similar appearance could be obtained with the other strains by making a stab culture in semi-solid medium.

*Solid media.*—Anaerobic cultures gave a fairly profuse growth in the presence of $CO_2$. Appearances were as follows:

(*a*) At twenty-four hours growth of all strains was of a flat mycelial type.

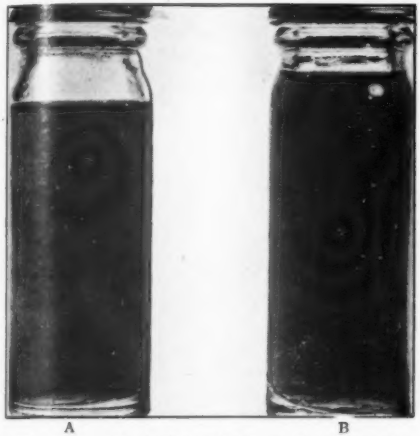
(*b*) After five to seven days: three possible types:

(i) (Strain I) Small rough colonies with the appearance of *A. israeli.*

(ii) (Strain IV) Rough flat colonies densely adherent to the medium, which grow up to 2 mm. diameter in seventy-two hours. The organisms were composed of coccal chains.

(iii) Other strains showed small smooth colonies up to 2 mm. diameter after five to seven days. These colonies were similar to the smooth colonies described by Rosebury (1944) in strains he isolated from actinomycotic lesions and from the mouth. Colonies were never pigmented (Fig. 4—Strain I).

After a number of subcultures the organisms grew more rapidly, provided the medium was varied at each subculture, and the colonies on solid media became rather larger and were similar in appearance



A B

FIG. 3.—A, Typical band of growth at junction of aerobic and anaerobic zones—Brewer's medium. B, Plume-like colonies in Brewer's medium.

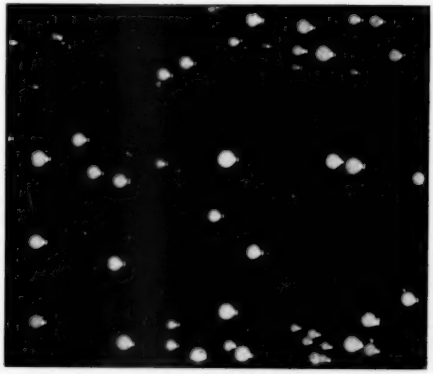


FIG. 4.—Smooth colonies of actinomyces. × 6.

to those of *A. naeslundi* described by Thompson and Lovestedt (1951). Strains IV and V showed a rough-smooth colony change, the change occurring in subcultures from either type of colony (Fig. 5—Strain V.R.).

*Broth.*—Strains I and III grow with a slight granular deposit and some turbidity.

Other strains show a deposit of hard floccules with no turbidity of medium, sometimes the rather typical cauliflower appearance described by Colebrook (1920) being present.

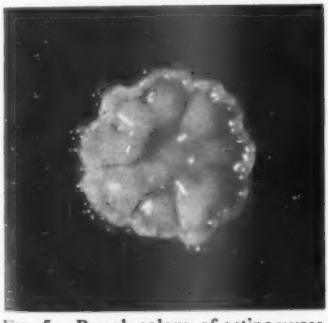


FIG. 5.—Rough colony of actinomyces. × 20.

FIG. 6.—Clumps of organisms from semi-solid media. Gram stain × 1,714.

## MORPHOLOGY

This varied with medium and time of incubation. Strains I and III may be considered together. In semi-solid and on solid media these had a typical clumped appearance rather like diphtheroids, and in smears distinct branching could be found particularly with nigrosin preparations (Fig. 6). This appearance was also found in broth during the first two weeks but after a further three weeks at room temperature long filaments appeared in broth cultures (Fig. 7).

Other strains show a similar appearance to Strains I and III except that no long filaments could be found at any time in broth cultures.

Strains IV and V are unlike any other strains as they are often coccoid in nature and may appear as chains of cocci although these chains always show evidence of budding (Fig. 8). In young cultures the diphtheroid appearances are found while in old cultures branching chains are formed. If, however, the colonies revert from rough to smooth the coccoid appearance is lost and the organism is found in the diphtheroid form.

FIG. 7.—Filamentous forms found after prolonged incubation in broth. × 1,714.

FIG. 8.—Branching chains of cocci found in strain IV. × 1,714.

## DISCUSSION

The confused descriptions of the actinomycotic organisms isolated from the lacrimal canaliculus make it seem probable that more than a single type of organism is the cause of lacrimal concretions. There is no doubt that this confusion is due to studies of only single strains or at the most two or three strains by various workers, and to the fact that these strains have not been studied over a period of time.

From the observations on our strains it seems that the organisms are most closely allied to the *Actinomyces israeli* (Waksman and Henrici, 1948) an admittedly heterogeneous group, the only alternative seeming to be to include them with Naeslund group C strains (*A. naeslundi*) but none of the strains are truly of this group since they grow poorly or not at all under aerobic conditions, although Morax (1905) has described strains which would grow aerobically.

It is remarkable that these organisms which can be highly pathogenic in certain situations localize in the canaliculus, but a similar condition does occur in the tonsil from which site Slack (1942) has isolated numerous *A. israeli* organisms from the concretions in tonsillar clefts. That these organisms are potentially invasive is substantiated by the observations of Chesneau (1908) and Gibson Moore (1952) both of whom have found a case in which the organisms invaded the lids from the canaliculus. At the moment we are unaware as to what is the reason for an Actinomyces becoming "invasive" or even whether it is a property of the host or the organism, but it seems that in the lacrimal canaliculus this power is the exception rather than the rule.

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[*November* 13, 1952]

# Macular Degeneration Treated with Cortisone

By H. E. Hobbs, F.R.C.S.

The accessibility of the anterior segment of the eye for purposes both of treatment, by drops or subconjunctival injections, and of observation, has led to extensive trials of cortisone in disease of this part of the eye. Many such types of ocular lesion have been found to be benefited by the use of this hormone (Duke-Elder, 1951*a*) and especially those inflammatory and allergic conditions which are characterized by markedly increased vascularity and exudation, among which iridocyclitis (Hobbs, 1951) and interstitial keratitis (Cook, 1951) may be given special mention as two in which the usual course of the disease may be dramatically interrupted by this form of treatment.

It was hoped that posterior segment lesions could be influenced in a similar way and the fact that immediate successes after local administration were not apparent led to trials with systemic treatment; but without anything like the consistently good results which have been seen in keratitis and iritis.

Disease of the macular region of the retina attracts particular attention both because of the disastrous effects of destructive lesions upon central vision and because, in a number of them, the lesion can be seen ophthalmoscopically to consist of an exudate and is believed to be associated with vascular anomalies of one sort or another.

Central serous retinopathy is one such condition of a relatively acute type, occurring predominantly in the younger age groups and showing with the ophthalmoscope a clearly demarcated area of œdema covering the macula. Here some observers claim prompt and complete recovery (McLean *et al.*, 1951; Gordon *et al.*, 1951; Woods, 1951, and others) whilst others have found the lesions to be unaffected by treatment (Agatston, 1951; Scheie *et al.*, 1951). On the whole, however, the œdematous exudate in this condition has been seen to absorb more rapidly under treatment than would have otherwise been expected—in one or two instances in a matter of hours. Of 20 cases reported in the American literature for 1951, 16 were considered to be thus improved and 4 only to have been unaffected. My own experience covers 5 cases, all treated by local injections and in these complete recovery was seen in a period which varied from twelve days to four weeks. In 3 of them I felt that the expected course had been shortened materially.

On the other hand when one turns to the more solid lesions of later life the picture is both more obscure and less encouraging. More obscure, because one is often uncertain as to the precise type of lesion which has been treated when the diagnosis is given simply as "macular disease" or "macular degeneration"; but if one accepts such cases as being senile pigmentary degeneration then, apart from a single case reported by Woods (1951) the results of treatment have been negative. With disciform degeneration of the macula, however, the picture is a little different. Many observers report that treatment is completely without effect on the lesions (Lavery *et al.*, 1951; Leopold *et al.*, 1951; Olson *et al.*, 1951; Fitzgerald *et al.*, 1951) and this has been my own experience with 3 cases I have treated. On the other hand a few find more hopeful signs in their results: McLean and his co-workers, for example, report 3 cases in which improvement was believed to have occurred to some extent; Gordon *et al.* (1951) recorded a visual improvement from 20/100 to 20/40 after systemic treatment with ACTH and Agatston (1951) one in which the retinal lesions appeared to become flattened and vision improved slightly. It is quite clear, however, that even the most sanguine of our American colleagues claims no such dramatic results as have been achieved with the more acute lesion of central serous retinopathy; but, on the other hand, if the hitherto inevitably hopeless prognosis of macular lesions in older people can be altered in any degree by treatment this would appear to be an opportunity not to be disregarded.

It is for this reason that I ventured to bring to the notice of the Section the case of Mrs. G. H., aged 66, who has appeared here for examination.

This is a patient who developed a circumscribed raised yellowish area at the left macula which became apparent during the latter part of 1950. She was first examined (by Mr. P. McG. Moffatt) on 10.1.51 when a film had been appearing over the sight of the left eye for some seven weeks. Vision with her lenses at that time was 6/5 right eye, 6/24 left eye. It was known that when she was provided with these lenses by an optician some months previously vision in the left eye had been normal.

Reaction at this time showed that, by the addition of a further ¾ dioptre sphere, vision in the left eye could be improved to 6/9, and examination of the fundus revealed a clearly circumscribed raised oval area at the left macula the nature of which was uncertain. The fundus in Fig. 1 shows the appearance of the lesion at this stage. There was, too, some "colloid" change at the right macula and although it was felt that a neoplasm in the left eye was a possibility this last finding suggested a disciform macular degeneration as the cause.

Mr. Moffatt kindly asked me to see the patient at this stage and we decided that a trial of cortisone was justified in view of the poor prognosis for left vision on either diagnosis and the possibility, if the lesion was, in fact, an exudative one and responded to treatment of definitely excluding a neoplasm. The central field at this time (19.1.51, Chart 1) showed a 4° absolute central scotoma to 2/2000 white.

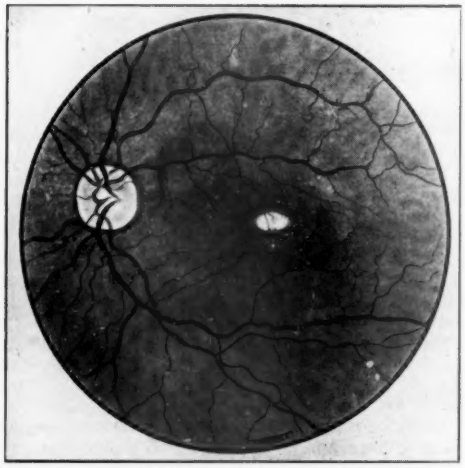

FIG. 1.—A macular lesion similar to that in the left eye, before treatment.

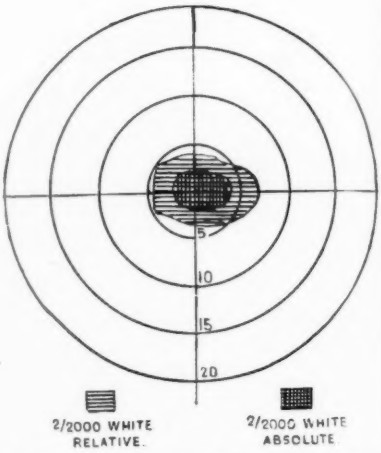


CHART 1.—Left central field (stereofixation) before treatment.

*Treatment* with cortisone by 20 mg. injections, either intratenonically or subconjunctivally, at twice weekly intervals was begun. After 4 injections, whilst a raised area at the macula was still discernible it was less clearly defined and the surrounding retina appeared œdematous with an overlying fine vitreous haze. Vision at this time (2.2.51), however, had fallen to less than 6/60 and the central field showed an absolute scotoma of rather more than 10° to 5/2000 white (Chart 2).

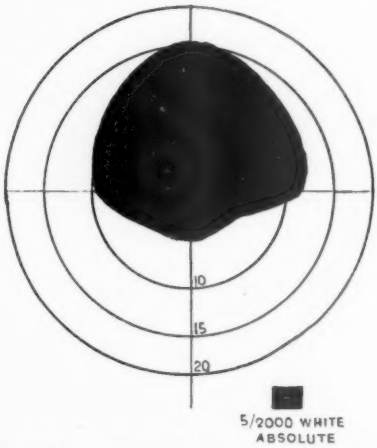


CHART 2.—Left central field after two weeks' treatment.

We considered that the fundus changes seen at this time represented some dissolution of the original solid-looking exudate and that the lesion was not neoplastic. The speed with which the changes had occurred was unexpected and was attributed to the cortisone. It was felt, therefore, that treatment might be expected to produce further changes in the same direction and that some recovery of macular function might thereby be produced. With the patient's agreement therefore treatment was continued.

After 4 more injections further changes in the fundus were seen. There was considerable œdema at the posterior pole extending over a larger area, but the central field at this time showed some improvement and visual acuity with a correcting lens had risen to 6/36. Two weeks later after a further 4 injections the appearances had altered somewhat and there was little sign of retinal œdema, the perimacular arterioles being clearly visible and the peripheral edge of the original œdematous area marked out by a fine deposit of whitish exudate, the whole resembling a miniature circinate retinopathy (Fig. 2, 2.3.51).

Vision had now improved to 6/18 + 2 although the central field (2.3.51) still showed a dense scotoma (Chart 3). Cortisone was gradually withdrawn from this time and no further improvement in central vision was seen. Although the field defect decreased somewhat in size, the exudate appeared to move centripetally from the macula and much of it absorbed.

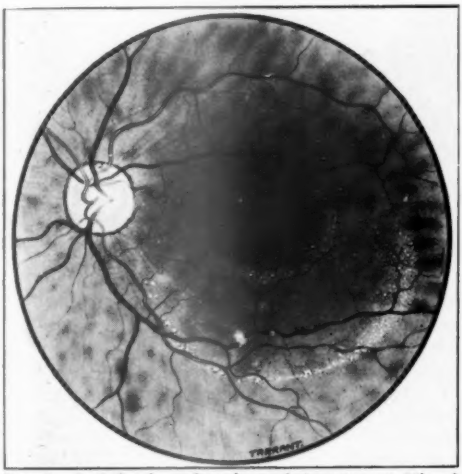

FIG. 2.—Left fundus, after six weeks' treatment. Visual acuity 6/18 + 2.

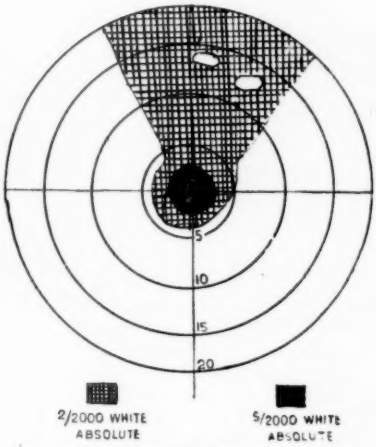


CHART 3.—Left central field after six weeks' treatment.

Some thirteen weeks later the patient complained of blurred vision in the right eye of a week's duration, and the visual acuity was found to have fallen in this eye to 6/60 with the development of a large central scotoma (Chart 4, 3.7.51); the fundus showed a large area of œdema at the posterior pole through which the mottled appearance of colloid bodies previously noted was visible (Fig. 3, 29.6.51).

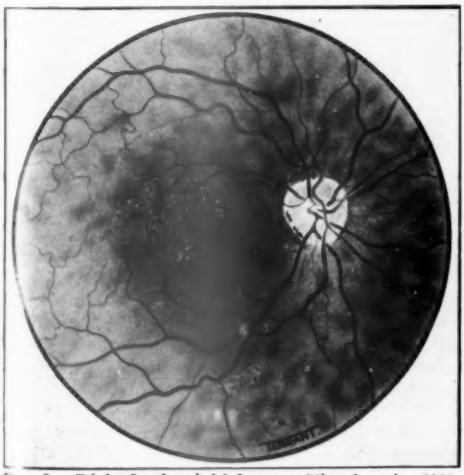

FIG. 3.—Right fundus, initial stage. Visual acuity 6/60.

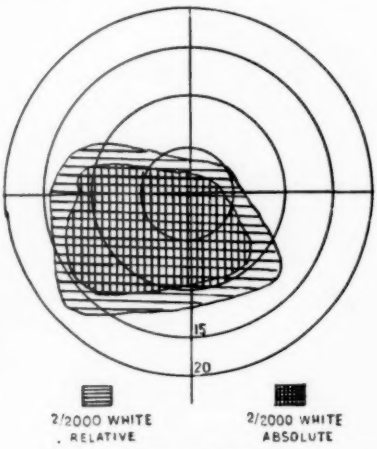


CHART 4.—Right central field before treatment.

Cortisone was begun at once in a dosage similar to that used in the left eye and a similar visual deterioration was noted in the first few weeks. The field (Chart 5) plotted on 16.8.51 shows an increase in the scotoma, and at this time visual acuity was 2/60 whilst the fundus showed a more clearly circumscribed yellowish-grey raised area with but little vitreous haze. The fundus appearance therefore more

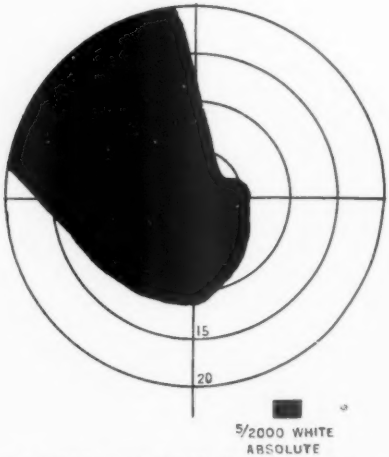


CHART 5.—Right central field after six weeks' treatment.

closely resembled that seen first in the left eye, and from this point matters began to improve, so that a week later visual acuity had risen to 6/24 with a corresponding improvement in the field. This improvement was maintained under further treatment and on 4.10.51 the scotoma was much smaller and less dense (Chart 6) and the fundus appearances resembled those in the stage of recovery in the left eye (Fig. 4, 1.10.51). Visual acuity at this time was 6/18, and with continued improvement it had risen to 6/9 by 17.1.52.

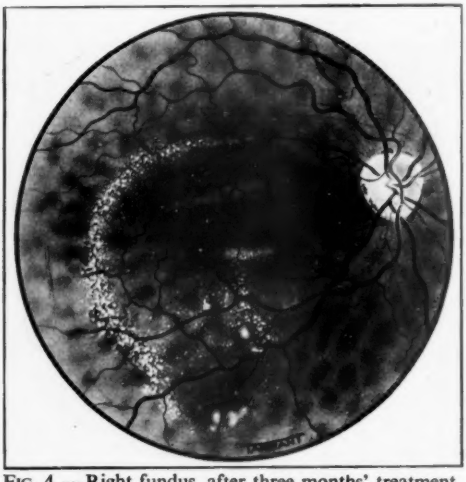

FIG. 4.—Right fundus, after three months' treatment. Visual acuity 6/18.

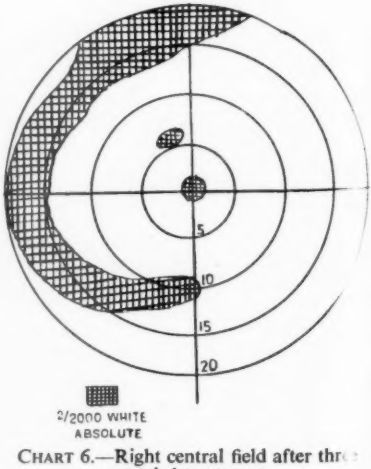


CHART 6.—Right central field after three months' treatment.

Unfortunately a relapse now occurred in the left eye and on 17.1.52 vision in this was 6/60. There was considerable macular œdema with fresh exudates and hæmorrhages and although some improvement (to 6/36) was seen after 50 mg. of cortisone subconjunctivally, retinal œdema remained and a

course of systemic cortisone (100 mg. a day for seven days) was tried. Little improvement was seen from this but a gradual absorption of the œdema occurred during the next three months at the end of which time vision had returned to its pre-relapse level of 6/18.

Since this time there has been very little change. Corrected vision remains at 6/6 in the right and 6/18 in the left eye; and the fundi (4.10.52) show little more than irregular pigment mottling at the maculæ and some traces of the circinate exudate (Figs. 5 and 6).

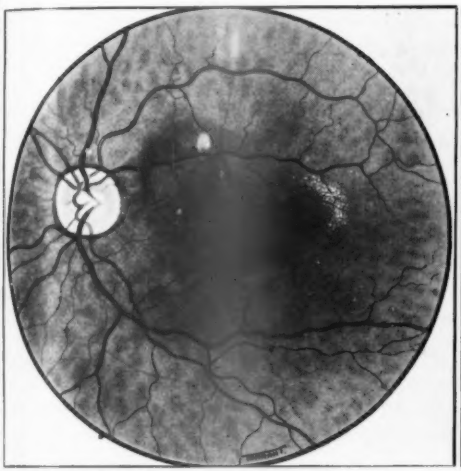

FIG. 5.—Left fundus, present appearance twenty-one months after beginning treatment. Visual acuity 6/18.

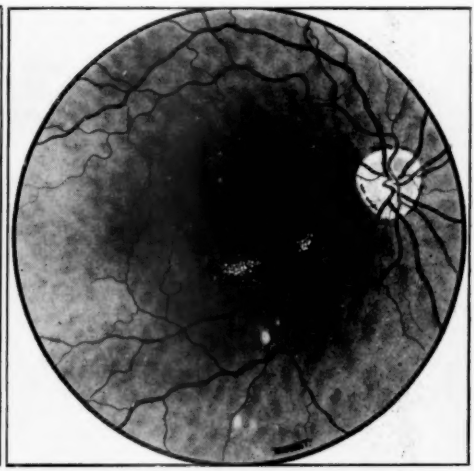

FIG. 6.—Right fundus, present appearance, fifteen months after beginning treatment. Visual acuity 6/6.

In the case of the right eye the improvement of vision from 6/60 to 6/6 under treatment is remarkable if not entirely unexpected, in view of the course in the left (and first affected) eye. However, to suggest that this is simply a success to be weighed against the many failures of treatment in disciform macular degeneration would, in my opinion, be misleading: it appears to me more likely that this response differs from those in other published cases because the fundus lesion itself, although disciform in appearance, arose as the result of a different pathological process.

The usual cause, in cases which have been examined histologically, has been found to be a hæmorrhage from the choriocapillaris extravasating between Bruch's membrane and the pigment epithelium (Duke-Elder, 1951*b*) and, indeed, evidence of this hæmorrhage is often to be seen during the fundus examination. No such hæmorrhages were visible in this instance and the response to treatment suggests to me that here the retina was raised to form the disciform swelling by a simple exudate of a serous nature. As far as I am aware such a condition has not been distinguished clinically from others of the exudative macular retinopathies grouped together by Junius and Kuhnt in 1926; but it is very interesting to find in the 1937 review, by Verhoeff and Grossman, of published cases of this type a case (their own number 3) which may well have been similar to that of Mrs. G. H. In this, too, a pale disciform swelling at the macula was found, in a man of 63, to be responsible for increasing blurring of vision over a period of five months. At that time the impossibility of excluding a macular neoplasm led to enucleation on the provisional diagnosis of sarcoma of the macula and the eye was thus available for histological examination. The result of this investigation was of considerable interest for it showed the macular swelling to have been caused by a subretinal exudate of pure serum without sign of hæmorrhage. Such a pathology suggested to Verhoeff and Grossman that this case provided a link between the more usual senile cases associated with a hæmorrhagic exudate and a poor prognosis for central vision, and those in which an exudative macular lesion of good visual prognosis is seen in younger individuals.

Such a comparison may also be valid, on the ground of their similar response to cortisone therapy, between central serous retinopathy and this form of disciform macular retinopathy; and in the case which I have described the favourable response may best be explained on the assumption that here, as in that of Verhoeff and Grossman, a serous exudate has been responsible for the disciform lesion.

It seems, therefore, that there is a case for distinguishing this type of lesion from the senile hæmorrhagic exudates at the macula, and I hope that, with further experience, this may be found

possible ophthalmoscopically. If, as is generally believed, all disciform macular lesions are produced by sclerosis in the underlying choroidal vessels it is unlikely that a permanent cure can be expected from treatment with cortisone. However, the facts that here, as in certain anterior segment lesions in which the prognosis has been improved by this form of therapy, the disease process is known to run a limited course and that it remains strictly confined to the macular area, leave room for hope that by a dissolution of the exudate at an early stage central vision may be preserved for some time. The course over a period of nearly two years of the case which I have described appears to me to provide some ground for this hope.

I should like to say how grateful I am to Mr. Moffatt for his help in the assessment of the case.

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**Mr. P. McG. Moffatt** said that a clergyman came to him complaining that he could no longer read the lessons. On examination, he was found to have a mixture of pigmentary degeneration and some organized exudate at both maculæ, and the left eye was rather worse than the right. With the left eye he could do no more than count fingers but with the right eye his vision was 6/60. He said how desperately he missed being able to read. It was suggested that he might have some injections of cortisone and he had had twelve of these. He came back to him only two or three days ago. The right eye, which previously had vision of 6/60, now had improved to 6/36, but what interested him even more was the improvement in the left eye which could see 6/60, and with + 6·0 added to each eye he could read J4. The patient was afraid to be too optimistic but he himself did feel that there had been some improvement.